TANDEM REACTIONS FOR THE SYNTHESIS OF OCTAHYDROISOINDOLES AND CHIRAL TETRAHYDROQUINOLINES

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PREFACE

A tandem S_N2-Michael addition sequence has been developed for the synthesis of six-five bicyclic nitrogen and sulfur heterocycles from ethyl ω-iodo-2-alkenoates. The preparation of nitrogen heterocycles involves the reaction of the iodoester with a primary amine and triethylamine in alcohol. This affords an intermediate which then cyclizes onto the acrylate acceptor to form the heterocyclic product. The formation of the sulfur heterocycles involves the reaction of the iodoester with thiourea to initially yield the isothiuronium halide adduct which is hydrolyzed in aqueous base to yield the sulfur heterocycle. The reactions proceed in good yields and are carried out in a single reaction flask. The mechanism and stereochemistry of the reactions are discussed and the structures have been elucidated by two-dimensional NMR methods.

A tandem one-pot reduction-reductive amination sequence has also been adapted for the construction of chiral tetrahydroquinolines using (-)-8-phenylmenthol as a chiral ligand. Diastereoselective monoalkylation was achieved by asymmetric induction of the ester of (-)-8-phenylmenthol and 2-nitrophenylacetic acid. The method involves alkylation of the benzylic carbon of the ester with an allylic halide, ozonolysis of the double bond to yield a nitro carbonyl compound and a tandem sequence involving reduction of the aromatic nitro group and condensation of the aniline or hydroxylamine nitrogen with the side chain carbonyl. The cyclized product is isolated as a single enantiomer in good yields. The mechanism and stereochemistry of the reactions are discussed and the structures have been elucidated by spectroscopic methods.

ACKNOWLEDGMENTS

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TABLE OF CONTENTS

Chapter Page

Chapter Page

LIST OF TABLES

LIST OF FIGURES

Figure Page

LIST OF PLATES

CHAPTER I

TANDEM REACTIONS INVOLVING THE MICHAEL ADDITION

Introduction

Tandem reactions are multistep transformations in which each subsequent step is determined by the preceding one. All the transformations occur under the same reaction conditions in a single laboratory operation. Several reviews[1-6] have described the use of tandem reactions in organic synthesis. Tandem reactions offer the advantage of forming several bonds in a single step to generate complex molecules, often with a high degree of stereoselectivity of the reaction.

Minimization of side products, a reduction in the amount of solvents and reagents, coupled with the decrease in the number of laboratory steps, provide for the economic and ecological justification for these types of processes. Tandem reactions are divided into anionic, cationic, radical, pericyclic, photochemical, and transition metal induced processes based on the first step of the mechanism of the reaction. The terms 'tandem', 'cascade', 'one-pot', 'one-flask', 'sequential', and 'domino' are used as synonyms for this class of reactions. Most tandem processes proceed through the formation of an anionic intermediate. Deprotonation of acidic -CH_2- or -CH- group in the substrate forms a

carbanion, which is followed by its reaction with an electrophile to form a new anionic intermediate. This intermediate can then attack a functional group within the same molecule (intramolecular) or in another molecule (intermolecular). The sequence is completed by trapping with an electrophile, such as H^+, or by elimination of a leaving group. In many cases, anionic transformations are either initiated or terminated by the Michael reaction.

Synthesis of Cyclopentanes

Urones and co-workers[7] have reported that esters of α, β, α', β'-diendioic acids can serve as substrates for anionotropic tandem reactions as shown in Figure 1. The intermediate enolate, generated in the first step by intermolecular conjugate addition of a nucleophile, attacks the second α,β-unsaturated ester group. The use of chiral nucleophiles in such conversions allows the preparation of optically active adducts. The reaction of homochiral lithium [(1*R*)-methylbenzyl]benzylamide (**2**) with dimethyl octa-2,6-dienedioate (**1**) resulted in cyclopentane derivative **3**. In this reaction, the configurations of the C-1 and C-2 atoms were entirely controlled; the configuration of the C-5 atom was controlled to a lesser degree, with the C-5 epimer **4** was produced in *ca* 5%.

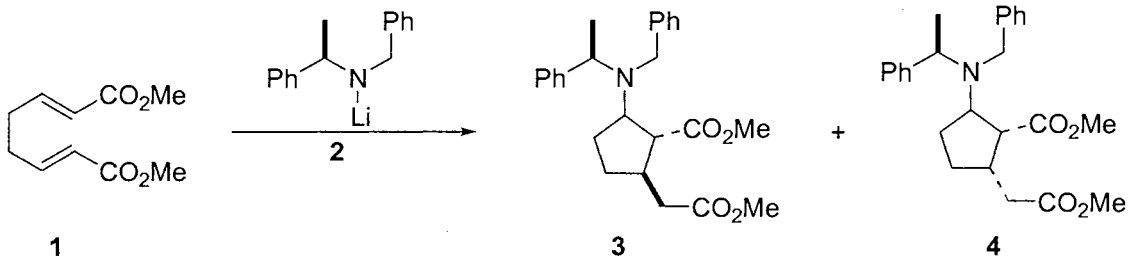


Figure 1. Synthesis of cyclopentane derivatives by anion-mediated tandem reactions.

Synthesis of a [3+2] Cycloadduct

Cyclopentanoid ring systems found in various natural products, such as prostaglandins, prostacyclines, and sesquiterpenoids, possess a wide range of biological properties. Yechezkel and co-workers[8] in their work on the synthesis of cyclopentanoid systems reported that 2-bromomethyl-3-phenylsulfonyl-1-propene (**5**), reacted with different alkenes to give [3+2] cycloadducts shown in Figure 2. The use of acyclic (*E*)-enoates in these reactions allows the preparation of stereohomogeneous *trans*, *trans* tri-substituted methylenecyclopentanes **7** in high yields. Furthermore, the tandem reactions of bromosulfone **5** with α,β-unsaturated esters containing the O atom in the γ position, with the (4*S*)-enoate **8**, proceeded with good selectivity. Subsequent ozonolysis of the alkene **9a** yielded the enantiomerically pure cyclopentanone **10**.

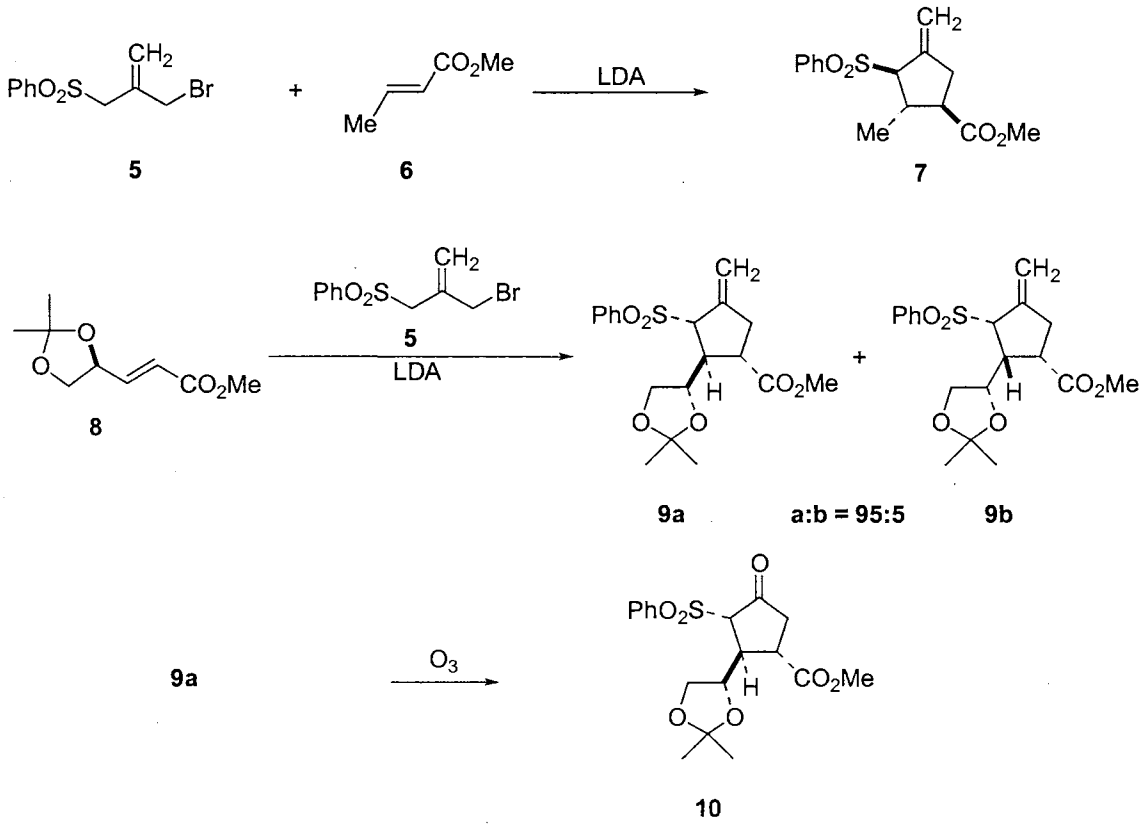


Figure 2. Tandem reactions of bromosulfone **5**.

Synthesis of 5-Membered Heterocycles

Five-membered heterocycles are usually encountered in structures of some bioactive compounds. Dumez and co-workers[9] reported that use of terminal alkynes enables one to change the order in which the reagents are entered into the reaction. In this case, the formation of five-membered heterocycles was seen to be favored as shown in Figure 3. The reaction of acyclic nitroalkene **11** with alkynol **12** afforded the tetrahydrofuran derivative **13**, and dihydropyran derivative **14** in a ratio of 1.7:1, while the aza-Michael addition reaction of *N*-methylprop-2-ynylamine (**15**) to nitroalkene **11** proceeded both regio- and stereoselectively to form 3-methylenepyrrolidine **16** as the only product.

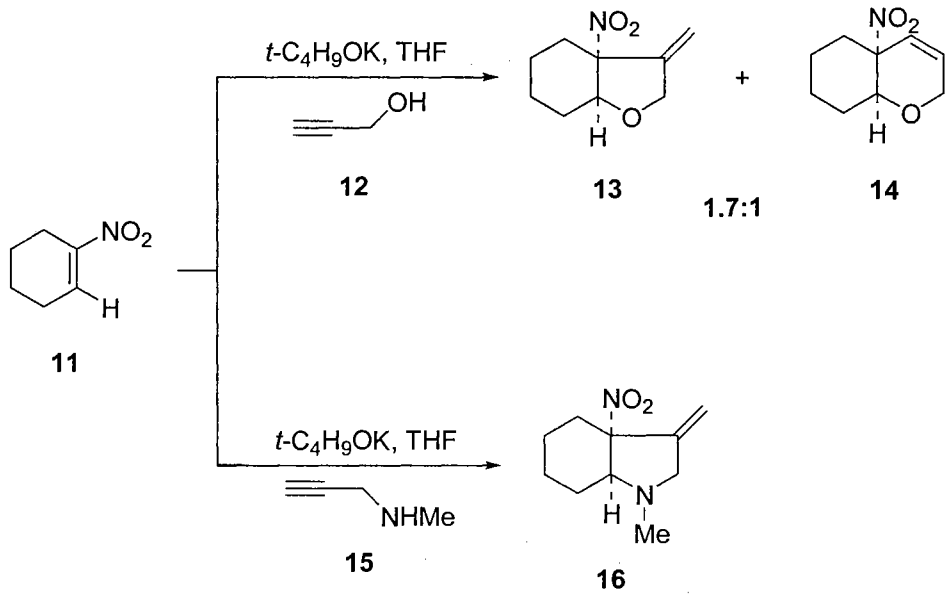


Figure 3. Synthesis of a tetrahydrofuran, dihydropyran and 3-methylenepyrrolidine.

Synthesis of Cyclohexylphosphonates

Alkylphosphonates are isosteric analogs of natural nucleotides and phosphates found in living systems. Alkylphosphonates are also useful precursors to olefins and chiral phosphine ligands. Naguoka and co-workers[10] have reported that organolithium

compounds initiate Michael cyclization of α,β,ψ,ω-unsaturated bisphosphonates. The addition of phenyllithium to a solution of tetraester **17** afforded a cyclic bisphosphonate **19** as shown in Figure 4.

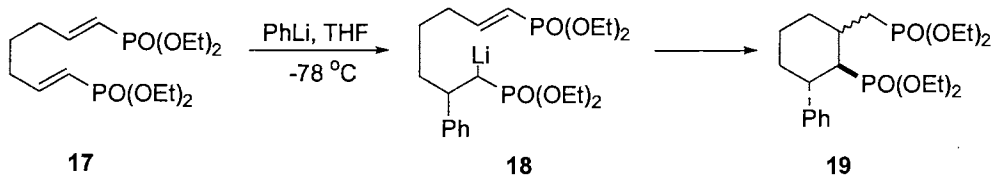


Figure 4. Synthesis of cyclic bisphosphonate.

Synthesis of Dihydropyridones

Enimines of 1-aza-1,3-butadiene derivatives are useful intermediates in natural product synthesis. Geirsson and co-workers[11] examined the synthetic potential of enimines in a two-step process involving the Michael addition followed by cyclization. When enimine **21** was reacted with methyl acetoacetate in the presence of catalytic amounts of LiI, unsymmetrically substituted 1,4-dihydropyridine **22** was formed as shown in Figure 5. When enimine **24** when reacted with methyl acetoacetate (**23**) in the presence of catalytic amounts of LiI, the cyclohexenone derivative **25** was produced (Figure 6). Hence, the reaction pathway depends on the structure of the enimine used. When the benzyl group in **21** was replaced by a *tert*-butyl group, as in **24**, the reaction followed another pathway to form the cyclohexenone derivative **25**. In these reactions, either two (path *a*) or three (path *b*), carbon atoms of the 1,3-dicarbonyl compound are involved in the formation of the six membered ring.

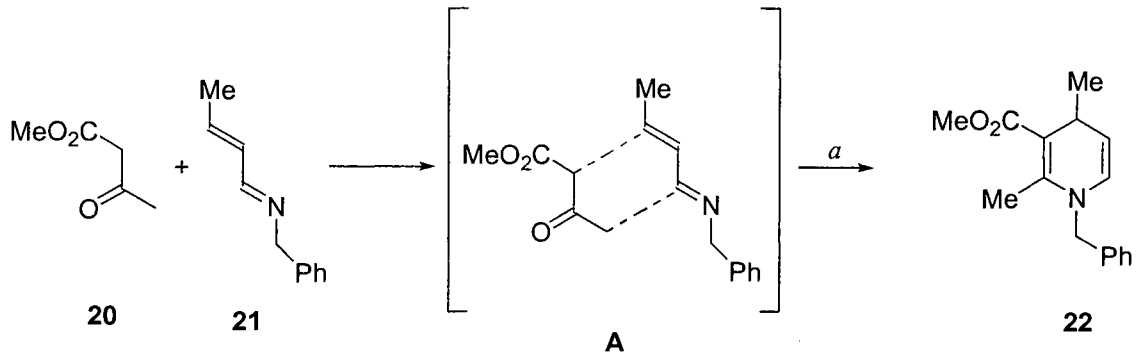


Figure 5. Synthesis of 1,4-dihydropyridines from enamine **21**.

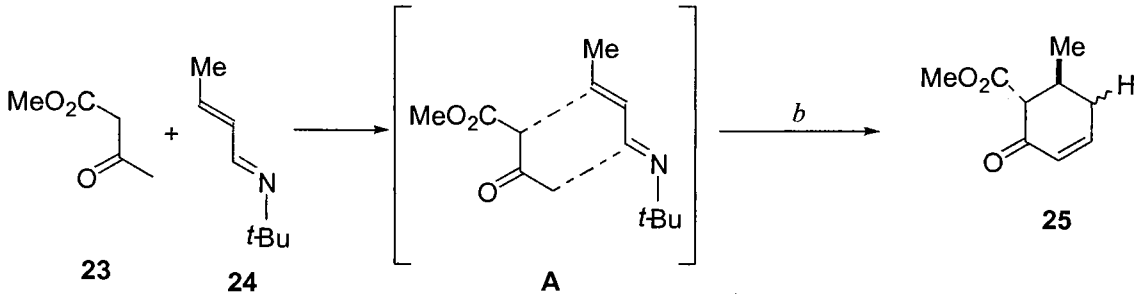


Figure 6. Synthesis of cyclohexenone **25** from enamine **23**.

However, the divergence was not observed when both enimines were reacted with 1,5-dimethyl-3-oxopentanedioate (**26**). Figure 7 shows the reaction of **26** with enamine **21**. Both enimines **21** and **24** formed derivatives of the bicyclo[3.3.1]nonan-3-one **27**, indicating that two molecules of the oxo diester are involved in the reaction. The authors further noted, that when the diester and the enimine were taken in a ratio of 2:1, product **27** was obtained in higher yield. The mechanism was speculated to involve the formation of an intermediate **B**, which then entered into a second Michael reaction which was followed by cyclization.

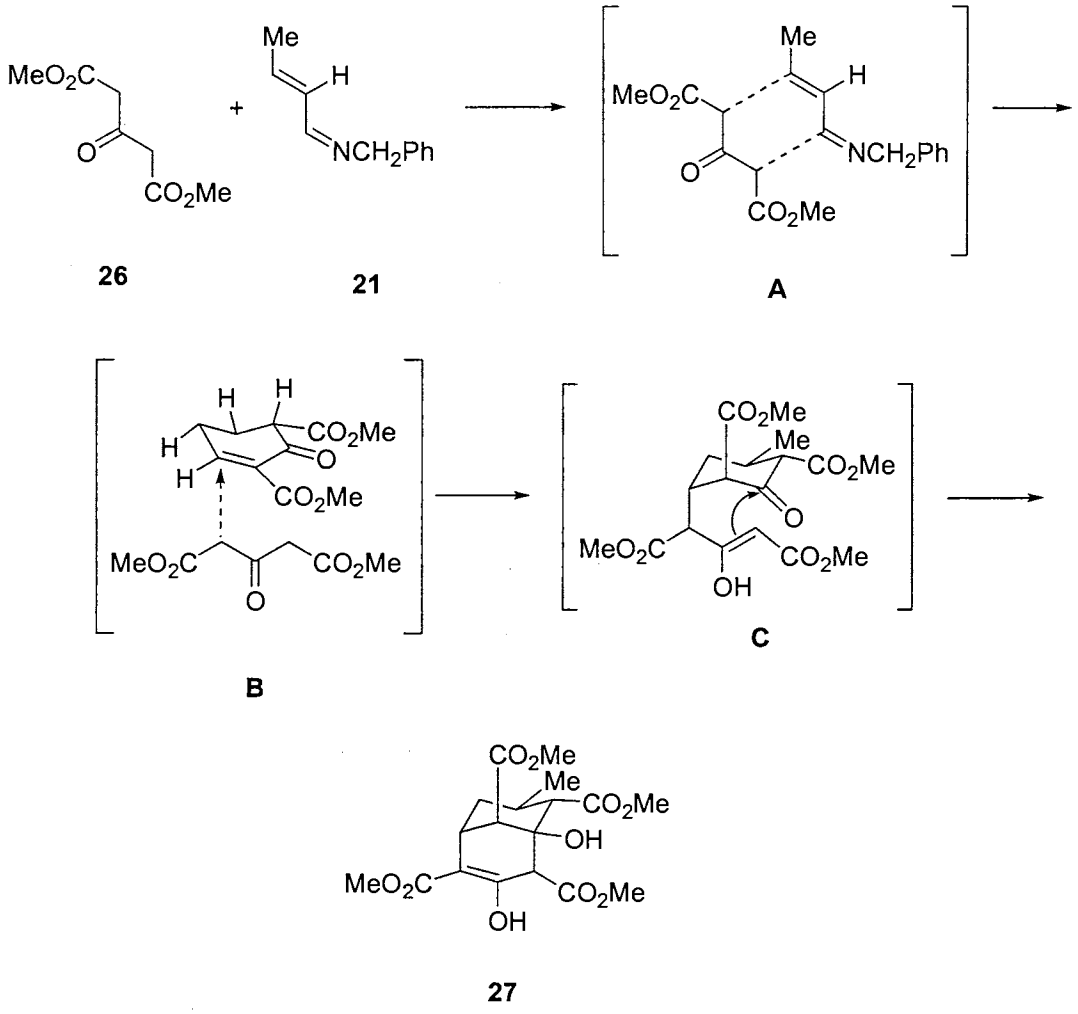


Figure 7. Reaction of enimines with dimethyl-3-oxoglutarate.

Synthesis of Bicyclic Heterocycles

Yakura and co-workers[12] synthesized furan derivatives by a double Michael addition reaction of 1-nitrocyclohexene (**28**) with alkynol **29** to yield the nitrooctahydrobenzofuran **30** as shown in Figure 8. The mechanism of the reaction probably involves the addition of the anion **31** across the double bond of nitrocyclohexene (**24**) and intramolecular cyclization of the resulting anion through species **A** and **B**. Subsequent protonation of the anionic intermediate resulted in a mixture of both *E* and *Z* isomers of **30** in a ratio of 55:45 (97%.

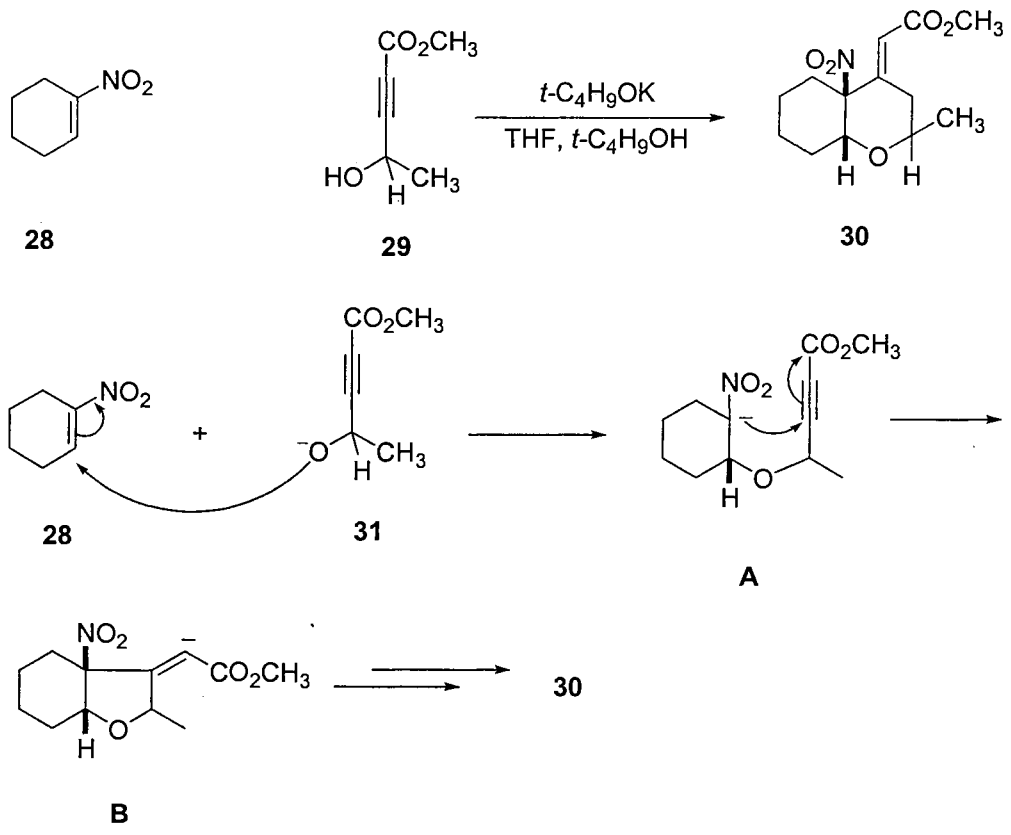


Figure 8. Synthesis of nitrooctahydrobenzofurans by double Michael addition.

Synthesis of Bicyclic Ring Systems

Bicyclo[2.2.2]- or bicyclo[3.2.1]octane systems are known to form an integral part in many natural products. Hagiwara and co-workers[13] reported that a double Michael addition makes it possible to construct the bicyclo[2.2.2]octane skeleton based on oxaphorone **32** which is found in many natural products. The reaction of oxaphorone enolate **33** with the α,β-unsaturated carbonyl compound **34** resulted in an intermediate **A** which underwent 6-*endo-trig* cyclization following path *a* to form product **35** exclusively. However, isomer **36**, which could be formed by either by a 5-*exo-trig* or 7-*endo-trig* cyclization by path *b*, was not detected according to the authors as shown in Figure 9.

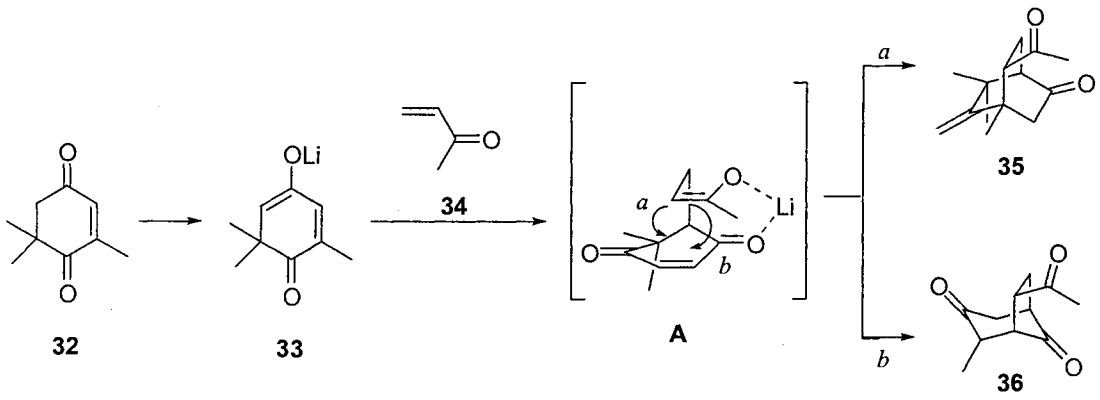


Figure 9. Double Michael Addition in the synthesis of bicyclo[2.2.2]octane.

In a series of papers,[14-17] Grossman and co-workers developed a new method for the construction of substituted polyfunctional cyclic compounds using the double Michael reaction of the tricyano ester **37** with 3-butyn-2-one (**38**) as shown in Figure 10.

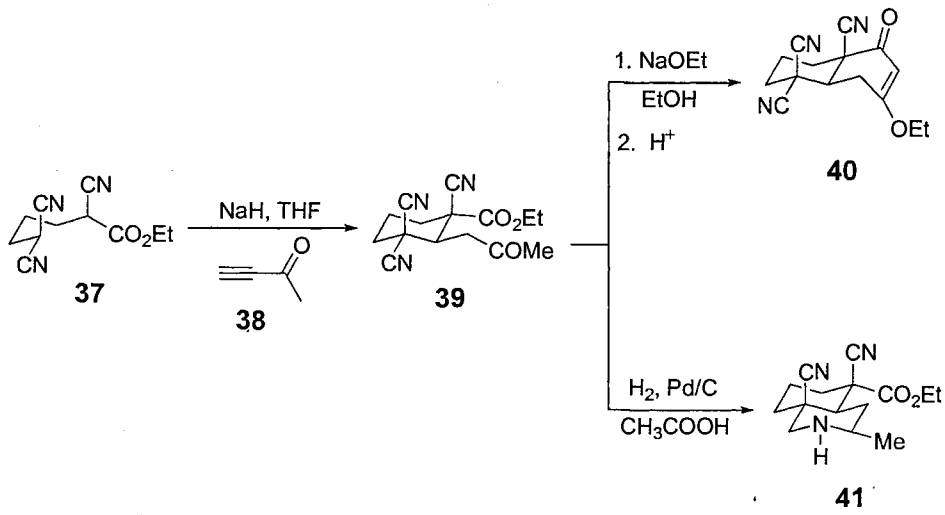


Figure 10. Grossman's method for the synthesis of polyfunctional cyclic systems.

Synthesis of Tricyclic Ring Systems

Barrett and co-workers[18] have developed a methodology for tandem 1,4-intermolecular and Michael addition reactions to synthesize pyrazolo[1,5-*a*]quinoline ring systems as shown in Figure 11. The key tricyclic synthon **44** was synthesized by the

reaction of quinolone **42** with methyl acrylate as shown in Figure 11. This synthon was used in the synthesis of fluoroquinolone antibacterial agents which were active against a large number of common pathogens.

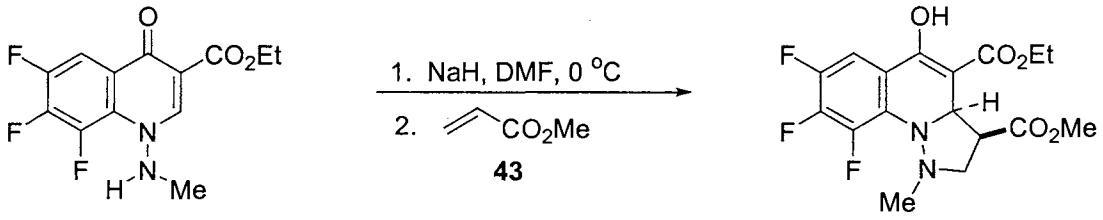


Figure 11. Synthesis of the pyrazolo[1,5-*a*]quinoline ring systems.

Takasu and co-workers[19] developed an intramolecular double Michael addition reaction for the total synthesis of the sesquiterpenoid fungicide (±)-culmorin (**47**), which has reported antifungal activity against fungi in wheat and corn. The tricyclo[6.3.3.0]undecan-10-one skeleton **46** was constructed in a single step by intramolecular cyclization of the cyclopentenone **45** by double conjugate addition as shown in Figure 12. Likewise, Ihara and co-workers[20] followed a similar strategy for the synthesis of (±)-8,14-cedranediol (**50**) via **48** to **49** to **50** as shown in Figure 13, although it differs mechanistically from the above reaction.

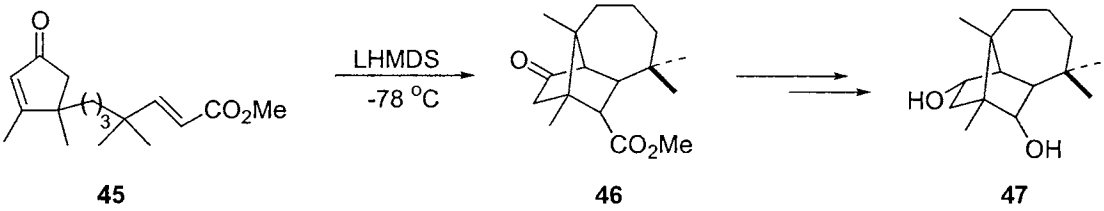


Figure 12. Synthesis of (±)-culmorin.

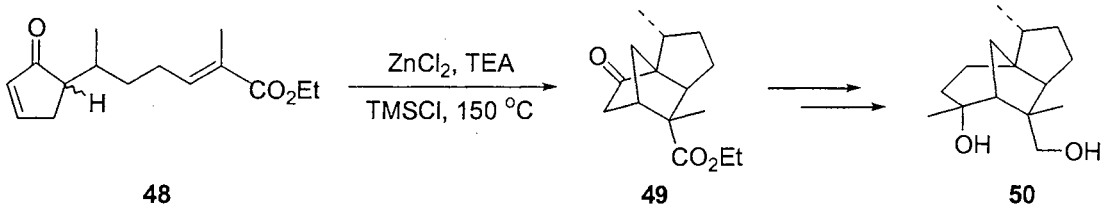


Figure 13. Synthesis of (±)-8,14-cedranediol.

Snider and co-workers[21] synthesized the alkaloid cyclindricine A (**53**) as shown in Figure 14. A Michael addition of ammonia to the conjugated diene system of ketone **51** afforded the perhydroquinoline **52**. Subsequent reaction of **52** with *N*-chlorosuccinimide and radical cyclization afforded a 55:45 mixture of **53** and its epimer, which were readily separated.

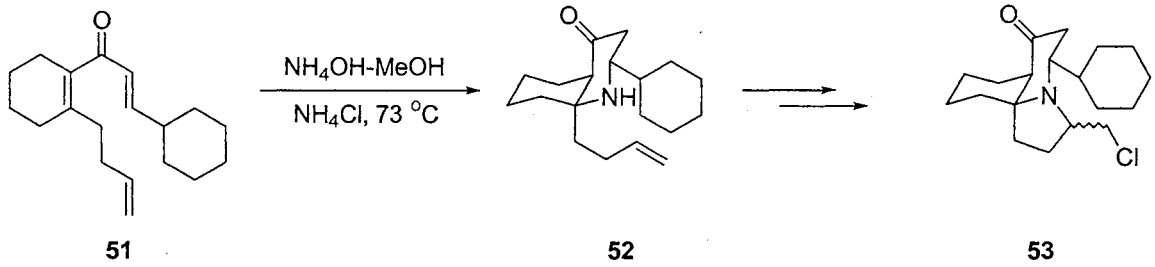
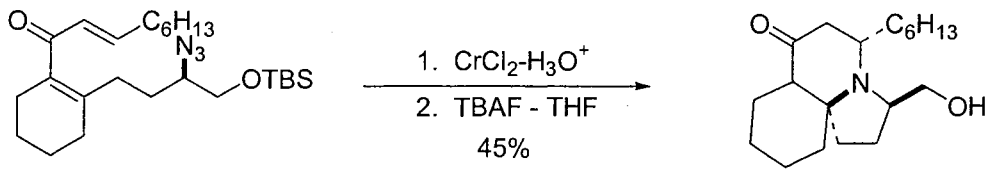


Figure 14. Synthesis of cylindricine A.

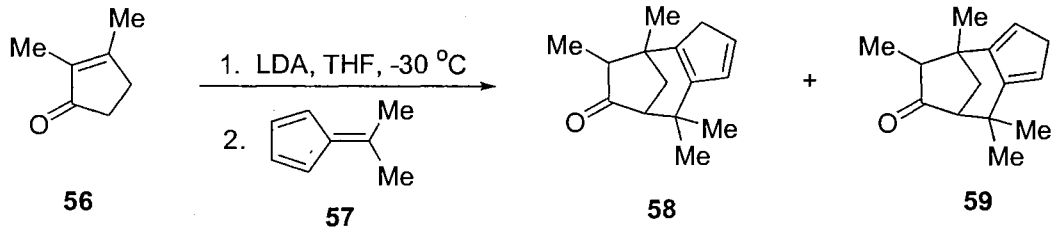
Cyclindricine C belongs to the family of Cylindricines A-J, which is known to inhibit growth of murine leukemia and human solid tumor cell lines. Molander and co-workers[22] synthesized (-)-cylindricine C (**55**) starting from the azide **54**. Selective reduction of **54** in presence of the diene system was carried out using $CrCl_2$. The resulting amine underwent a convergent and efficient double Michael addition reaction as shown in Figure 15.



54 **55**

Figure 15. Synthesis of cylindricine C.

Hong and co-workers[23] have shown that the double conjugate addition of enone **56** to the fulvene **57** offers a convenient approach to the tricyclo[5.3.0]alkane system. The dienolate generated from the enone entered into a Michael reaction with the fulvene to form an anionic intermediate, which underwent cyclization by an intramolecular Michael reaction to form tricyclic ketones **58** or **59** as shown in Figure 16. Furthermore, it has been reported[23] that the reaction is highly efficient with the use of cyclopentenone as the Michael acceptor.



56 **57** **58** **59**

Figure 16. Double Michael addition to synthesize tricyclo[5.3.0.n]alkane systems.

Gunawardena and co-workers[24] reported the stereoselective synthesis of tricyclo[5.3.1.0]undecane-4,12-dione (**63**) based on inter- and intramolecular Michael reactions of 1-pyrrolidinocyclohexene (**60**) with mesylate **61** as shown in Figure 17.

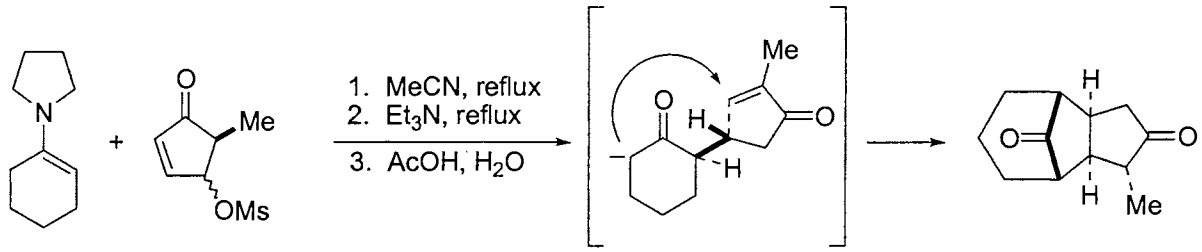


Figure 17. Stereoselective synthesis of a tricyclic undecane.

Synthesis of Tetracyclic Ring Systems

Hadjiarapoglou and co-workers[25] reported Michael reactions of methyl (chloro) cyclopropylideneacetate with cyclic dienolates formed from enones **64** and **67**. These reactions gave rise to tricyclic products **66** and **68**, respectively, as shown in Figure 18.

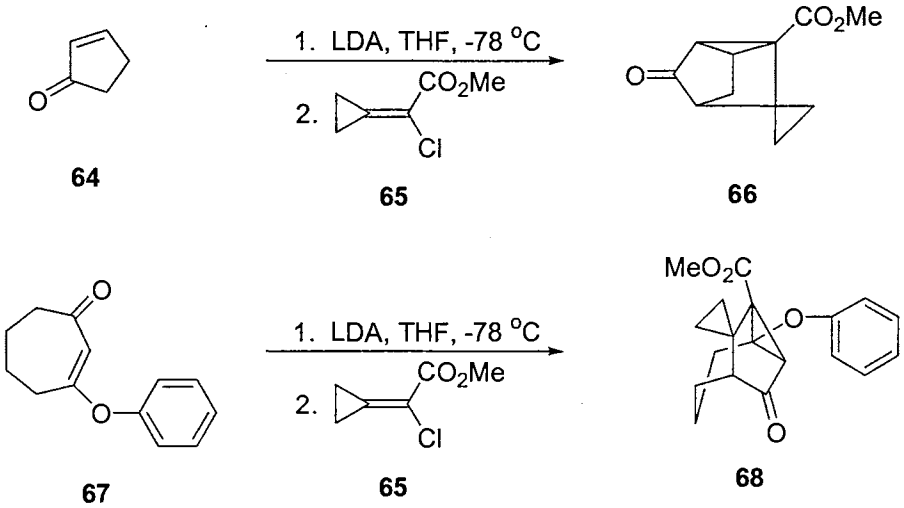


Figure 18. Synthesis of tricyclic adducts.

Erguden and co-workers[26] have reported tandem reactions which gave rise to angular polyquinanes. Tricyclic bisenone **69** was subjected to an intramolecular cyclization initiated by PhS^- as shown in Figure 19. Enolate **70** formed in the first intermolecular Michael reaction underwent a second intramolecular transannular Michael cyclization to

form the angular polyquinane **72** as shown in Figure 19. Presumably intermediates **70** and **71** were involved.

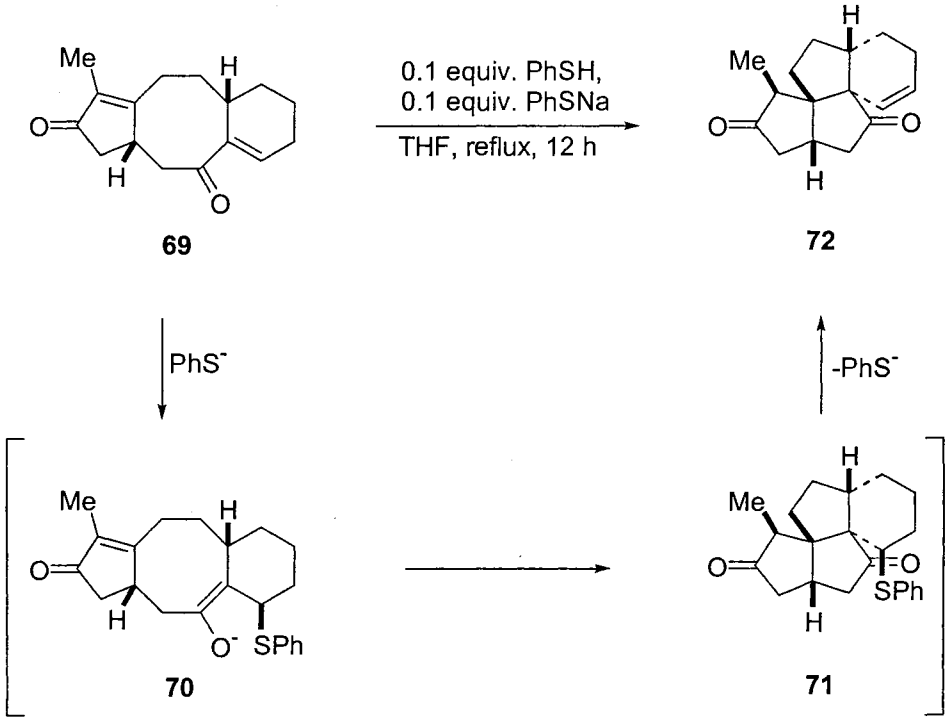


Figure 19. Synthesis of angular polyquinanes.

CHAPTER II

A TANDEM S_N2-MICHAEL ADDITION ROUTE TO SIX-FIVE BICYCLIC NITROGEN AND SULFUR HETEROCYCLES

INTRODUCTION

Many natural products[27-30] used as medicinal agents[31-35] incorporate one or more heterocyclic rings. The synthesis of heterocycles has over the years received a lot of attention in terms of developing efficient and elegant synthetic methodology. Boeckman and co-workers[36] reported a tandem Gabriel amine synthesis-Michael addition sequence for the preparation of dihydroisoindole **5** enroute to the natural product lycorine, which is an anti-cancer agent. Their approach, shown in Figure 20, involved the mild hydrazinolysis of phthalimide derivative **3** to yield the primary amine **4**, which was then cyclized by Michael addition reaction to afford the dihydroisoindole **5** in 70% yield.

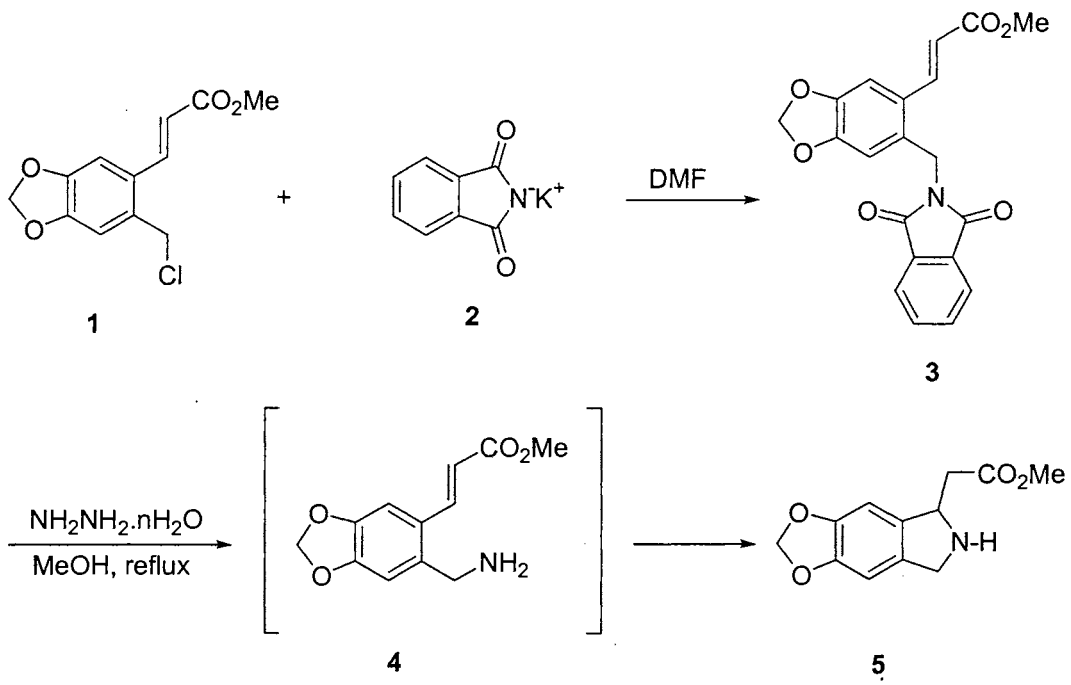


Figure 20. Boeckman's approach for the preparation of dihydroisoindole derivative **5**

Based on this result, in the present work, it was hypothesized that a similar approach involving a tandem S_N2-Michael addition sequence between ω-iodo-2-alkenoates **6** (cis or trans) and benzylamine could result in six-five fused bicyclic nitrogen heterocycles **7** (cis or trans) bearing a side chain functionality at the C2 position of the heterocyclic ring as shown in Figure 21.

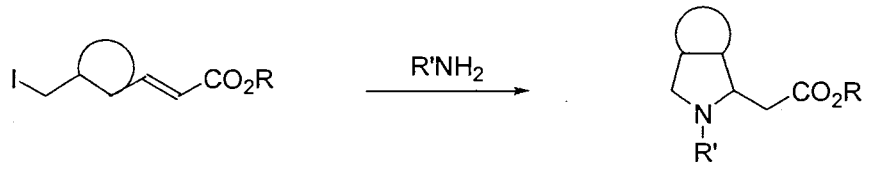
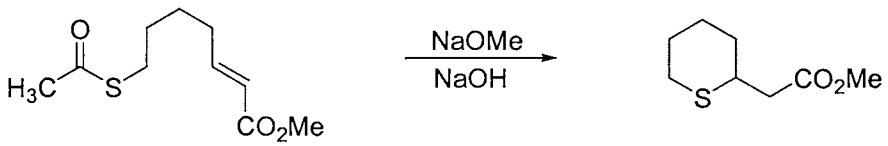


Figure 21. A tandem S_N2-Michael addition approach to prepare nitrogen heterocycles.

Since the fused rings would be saturated, it would present an interesting opportunity to study the stereochemistry of the cyclized products to determine the selectivity of the reaction. Consequently, in this study the topics of interest were: 1) the

stereochemical outcome of the reaction in terms of selectivity for the formed product, and 2) the orientation of the side chain with reference to the bridgehead hydrogens of the fused-ring system.

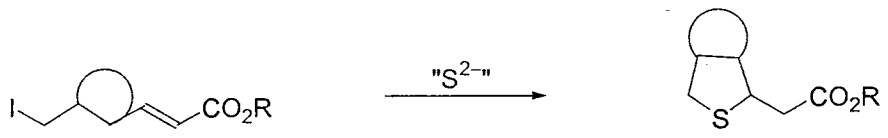
A tandem thioacetate methanolysis Michael addition sequence for the preparation of a tetrahydropyran derivative **9** from the thioacetate derivative **8** has been reported by Vedejs and coworkers[37] as shown in Figure 22. This methodology involved the treatment of **8** with methanolic sodium methoxide to yield the thiolate intermediate which then cyclized onto the acrylate moiety by a Michael addition to afford product **9**.



8 **9**

Figure 22. Vedejs and co-workers' approach for the preparation of sulfur product **9**.

Based on this result, it was hypothesized that a similar approach involving a tandem S_N2-Michael addition sequence resulting from the reaction between haloester **10** (cis or trans) and a source of sulfur could result in six-five fused ring bicyclic sulfur heterocycles **11** (cis or trans)bearing a side chain functionality at C2 position on the heterocyclic ring as shown in Figure 23.



10 **11**

Figure 23. A tandem S_N2-Michael addition approach for preparing sulfur heterocycles.

It was felt that the synthesis of substrate **12** should allow access to the cis, six-five fused nitrogen and sulfur heterocycles **13** as shown in Figure 24. Similarly the synthesis of substrate **14** should allow access to the trans six-five-fused nitrogen and sulfur heterocycles **15** as shown in Figure 24 where X = either N or S.

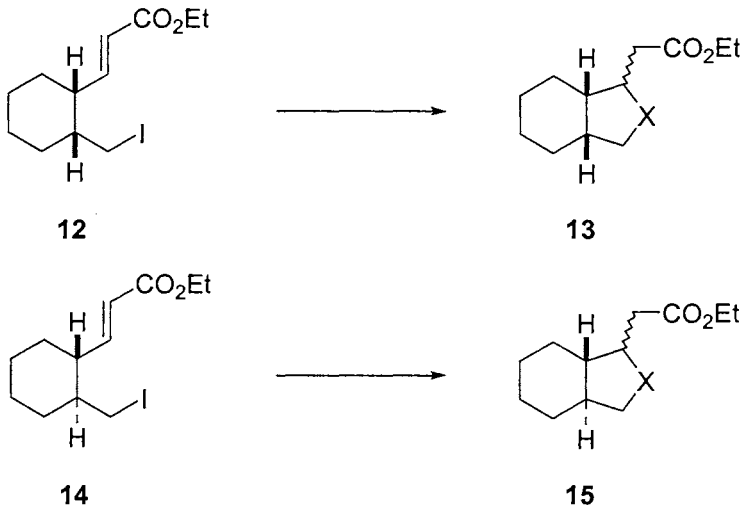


Figure 24. Preparation of cis and trans six-five fused ring nitrogen and sulfur heterocycles from **12** and **14**, respectively.

RESULTS

Synthesis of Heterocyclization Substrates

The synthesis of the cis heterocyclization substrate is shown in Figure 25. Reduction of the commercially available *cis*-cyclohexanedicarboxylic acid anhydride (**16**) with lithium aluminum hydride[38] in tetrahydrofuran yielded the *cis* diol **17** in 95% yield. The cis diol **17**, was then subjected to an oxidation using IBX (iodosobenzoic acid) in DMSO as per the procedure of Corey and Palani[39] to afford the cis lactol **18** in 80% yield. The selectivity of the oxidation reaction could be attributed to the fact that IBX is a mild oxidizing agent, and hence the reaction stops at the lactol stage rather than at the lactone stage. Wittig olefination of **18** with ethyl (triphenylphosphoranylidine) acetate afforded the afforded the cis hydroxy ester **19** in 47% yield. Reaction of **19** with methanesulfonyl chloride in the presence of triethylamine[40] in methylene chloride at 0 °C yielded mesylate **20**, which was reacted with sodium iodide in acetone to afford the cis iodo[41] ester **12** in 28% overall yield.

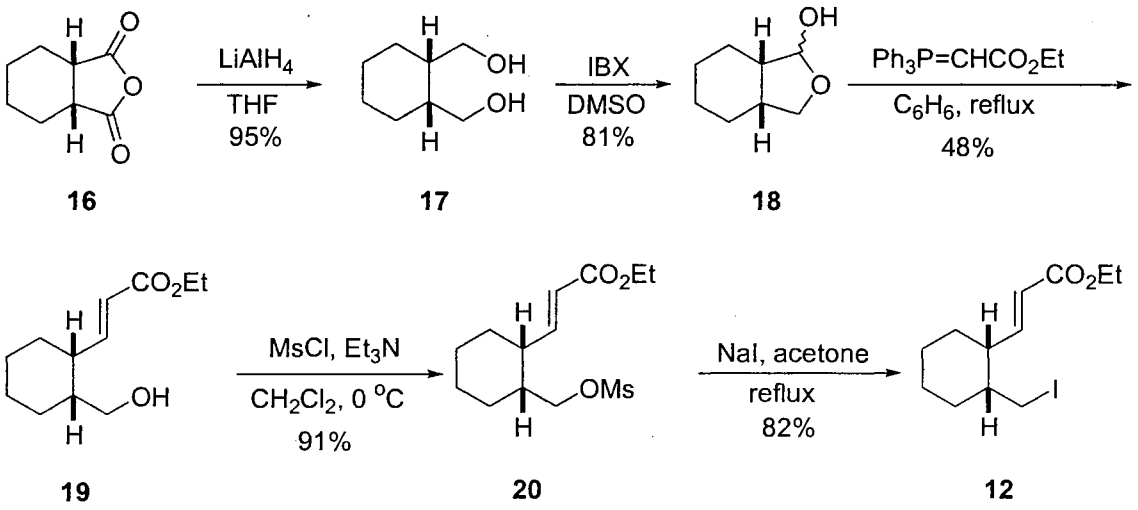


Figure 25. Synthesis of substrate **12**.

For the trans substrate, Diels Alder reaction of butadiene sulfone (**21**) and diethyl fumarate (**22**) under pressure afforded the trans cyclohexene diester **23** in 80% yield.[42] Hydrogenation of the cyclohexene double bond over 5% palladium-on-carbon in ethanol afforded the trans diester **24** which was reduced with lithium aluminum hydride in tetrahydrofuran and yielded the trans diol **25** in an overall yield of 93%. Using the same reaction sequence outlined for the cis precursor, the trans iodo ester **14** was prepared from **26** in 24% yield for four steps.

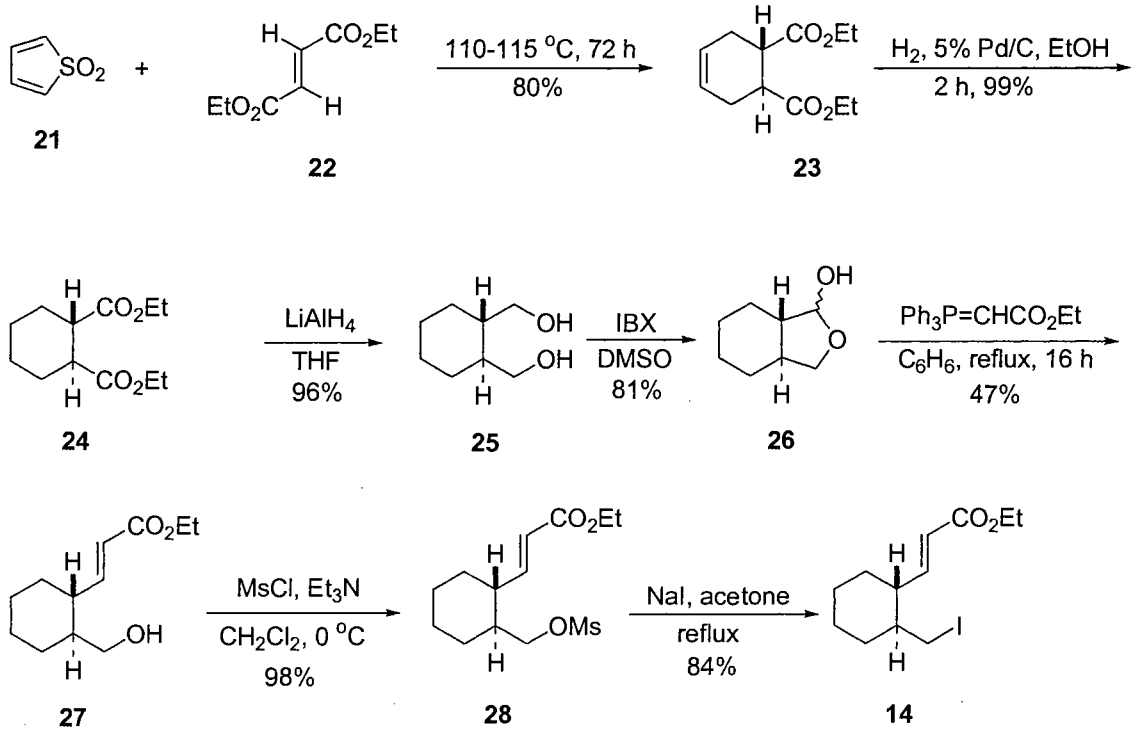
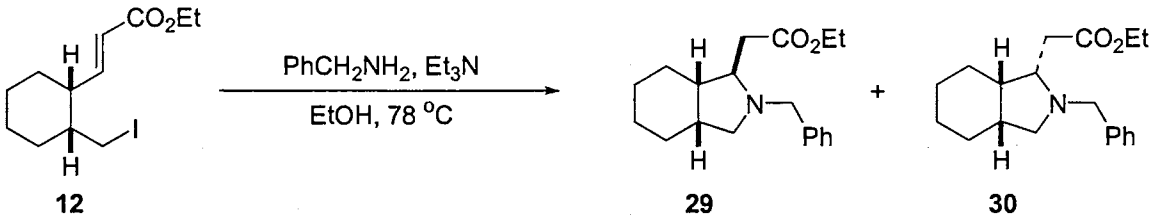


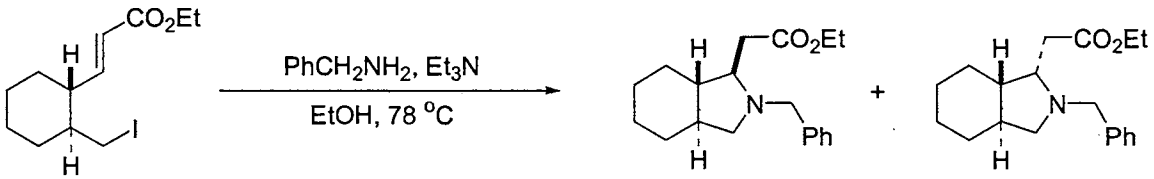
Figure 26. Synthesis of substrate **14**.

Preparation of six-five fused-ring bicyclic nitrogen heterocycles. Reaction of the cis iodo ester **12** with an equimolar amount of benzylamine in the presence of triethylamine in ethanol afforded the cis six-five fused-ring nitrogen heterocycles **29** and **30** in 74% yield as shown in Figure 27. Similarly, reaction of the trans iodo ester **14** with an equimolar amount of benzylamine in the presence of triethylamine in ethanol afforded the trans six-five fused-ring nitrogen heterocycles **31** and **32** in 76% yield as shown in Figure 28.



12 **29** **30**

Figure 27. Synthesis of cis six-five fused-ring nitrogen heterocycles.



14 **31** **32**

Figure 28. Synthesis of trans six-five fused-ring nitrogen heterocycles.

Structure Elucidation of Nitrogen Heterocycles 29, 30, 31 and 32. Initially proton cross peaks were assigned from the COSY-45[43] spectrum. In the NOESY[43] spectrum of the major cis product **29**, correlation of the side chain methylene protons with the protons on C7a and C3a established that the C1 acetic acid residue was cis to both bridgehead hydrogens. In the case of minor cis product **30**, a correlation between the protons on C1

and C7a was observed. This C1-C7a correlation established the cis orientation of the hydrogens on C1 and C7a. Moreover, the correlations between the side chain methylene protons and C7a were not observed. This suggests that the C1 acetic acid residue is trans to the C7a hydrogen.

For the major trans product **31**, the C1 proton was seen to be trans to the adjacent C7a hydrogen but cis to the C3a hydrogen. In case of the minor trans product **32**, the correlation between the protons on C1 and C7a confirmed that the acetic acid side chain was trans to the C7a hydrogen. Correlations were also noted between the bridgehead protons in products **29** and **30**, establishing the cis relationship between the bridgehead protons. Such correlations were not seen in trans fused products **31** and **32**.

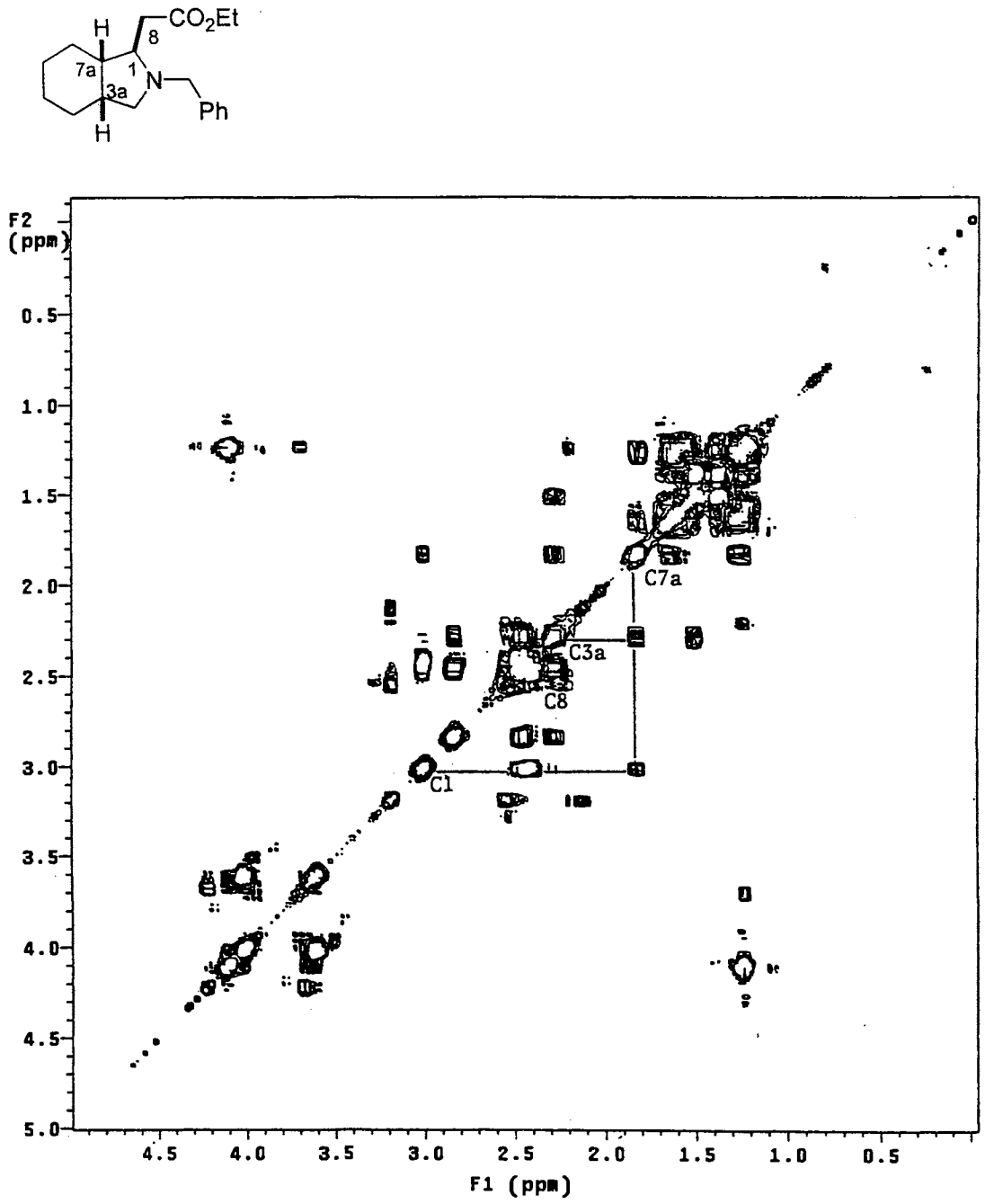
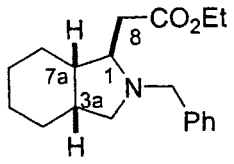


Plate I. COSY-45 of Ethyl (±)-(1*R**,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**29**)



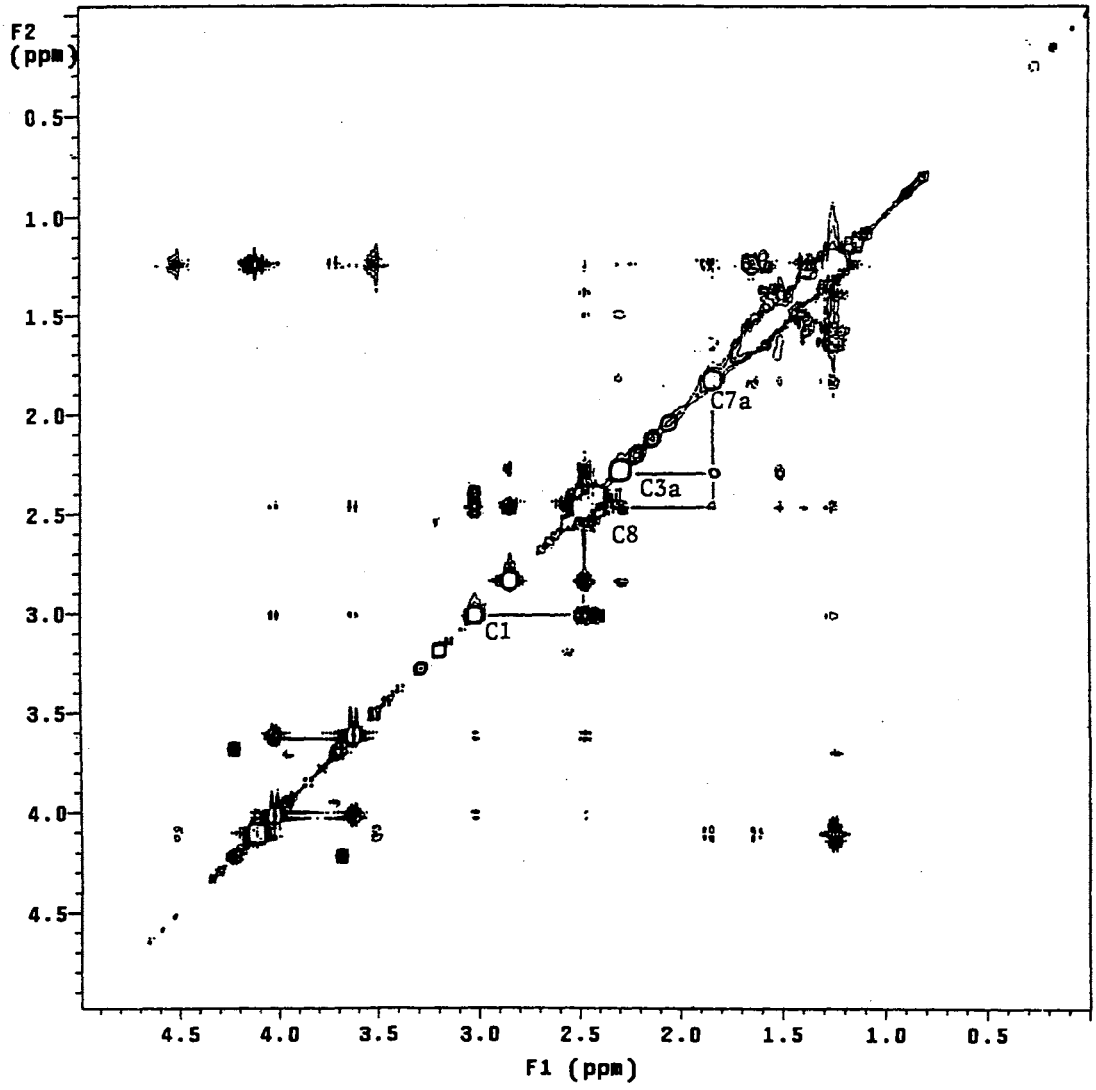


Plate II. NOESY of Ethyl (±)-(1*R**,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**29**)

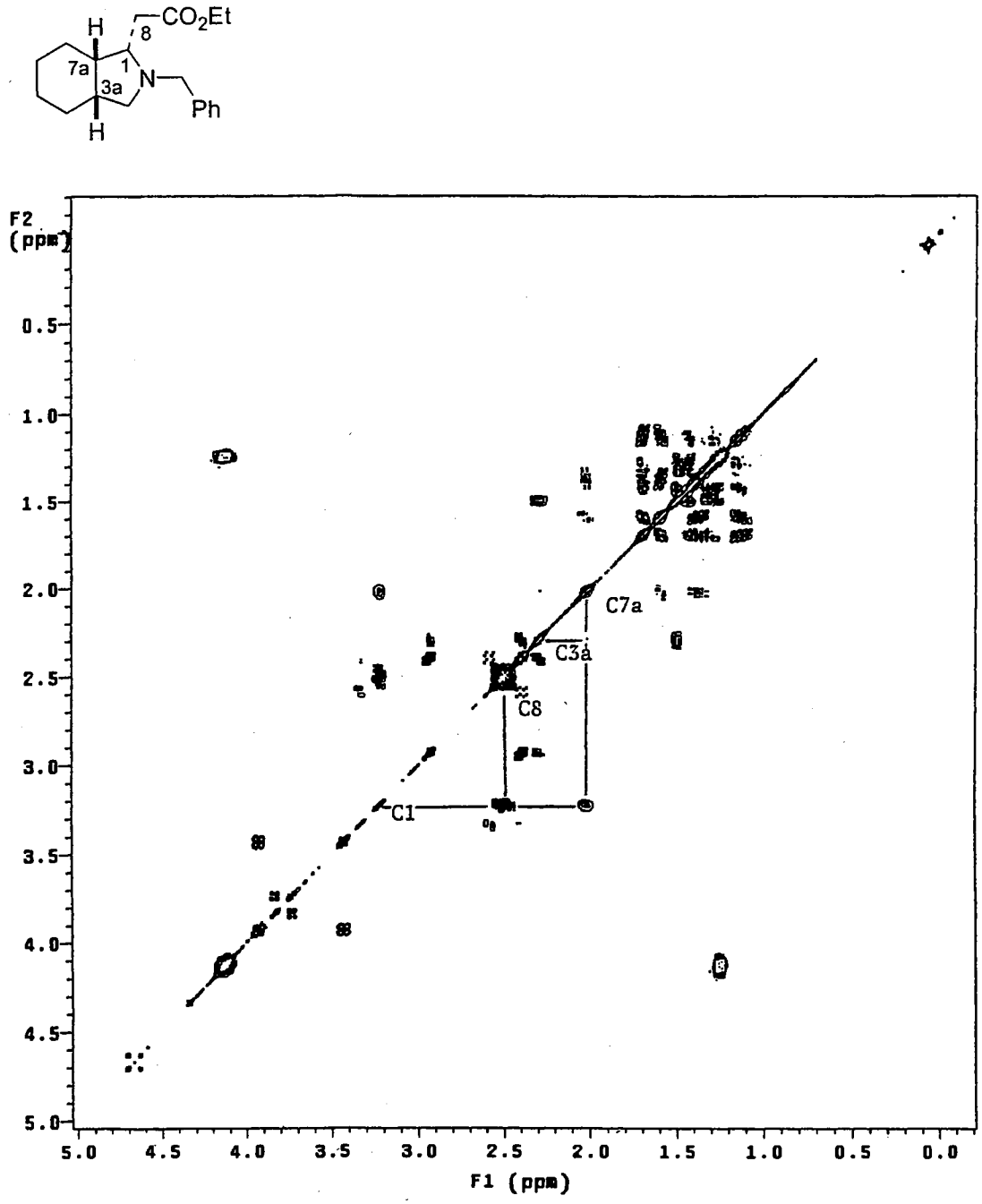


Plate III. COSY-45 of Ethyl (±)-(1*S**,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**30**)

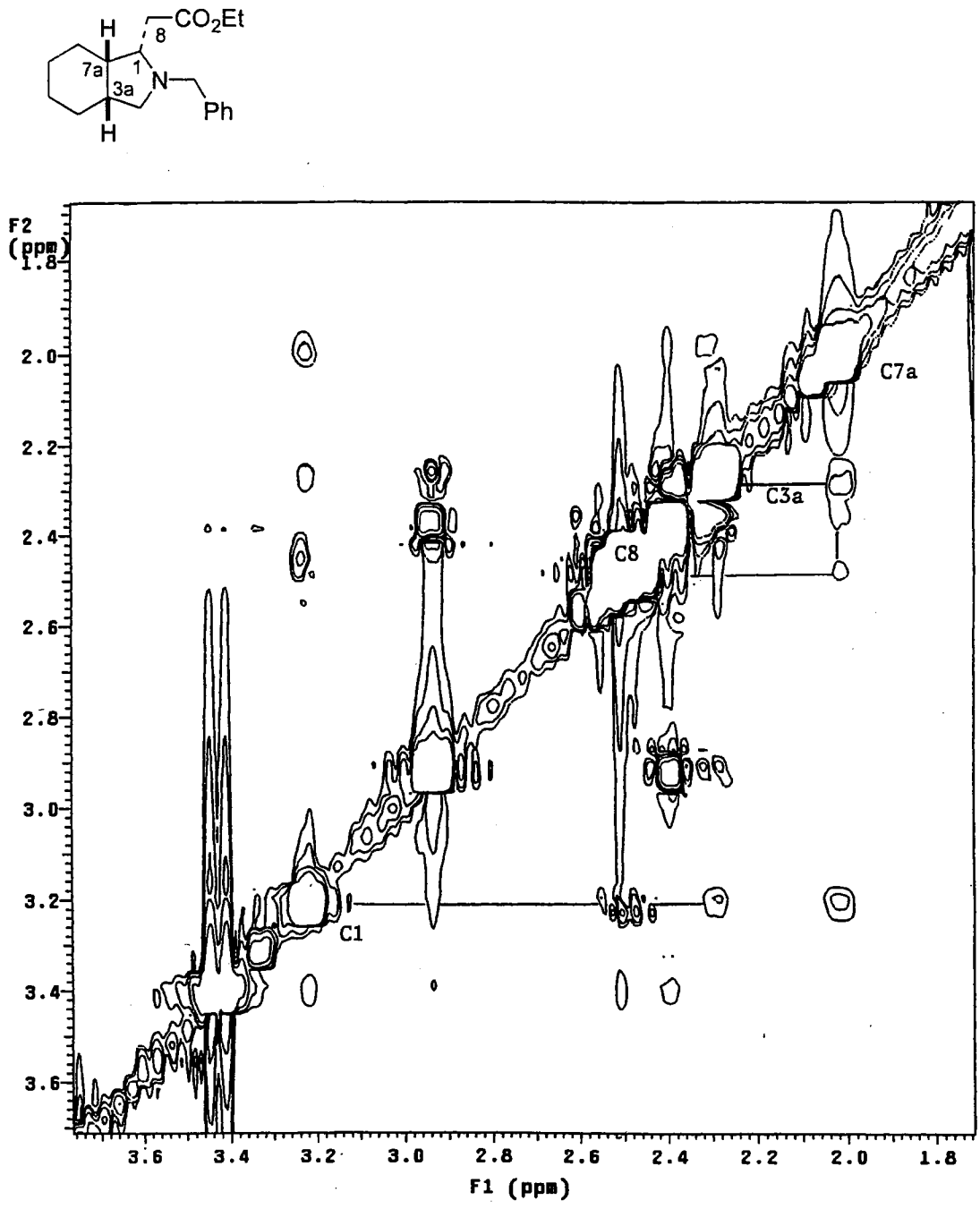


Plate IV. NOESY of Ethyl (±)-(1*S**,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**30**)

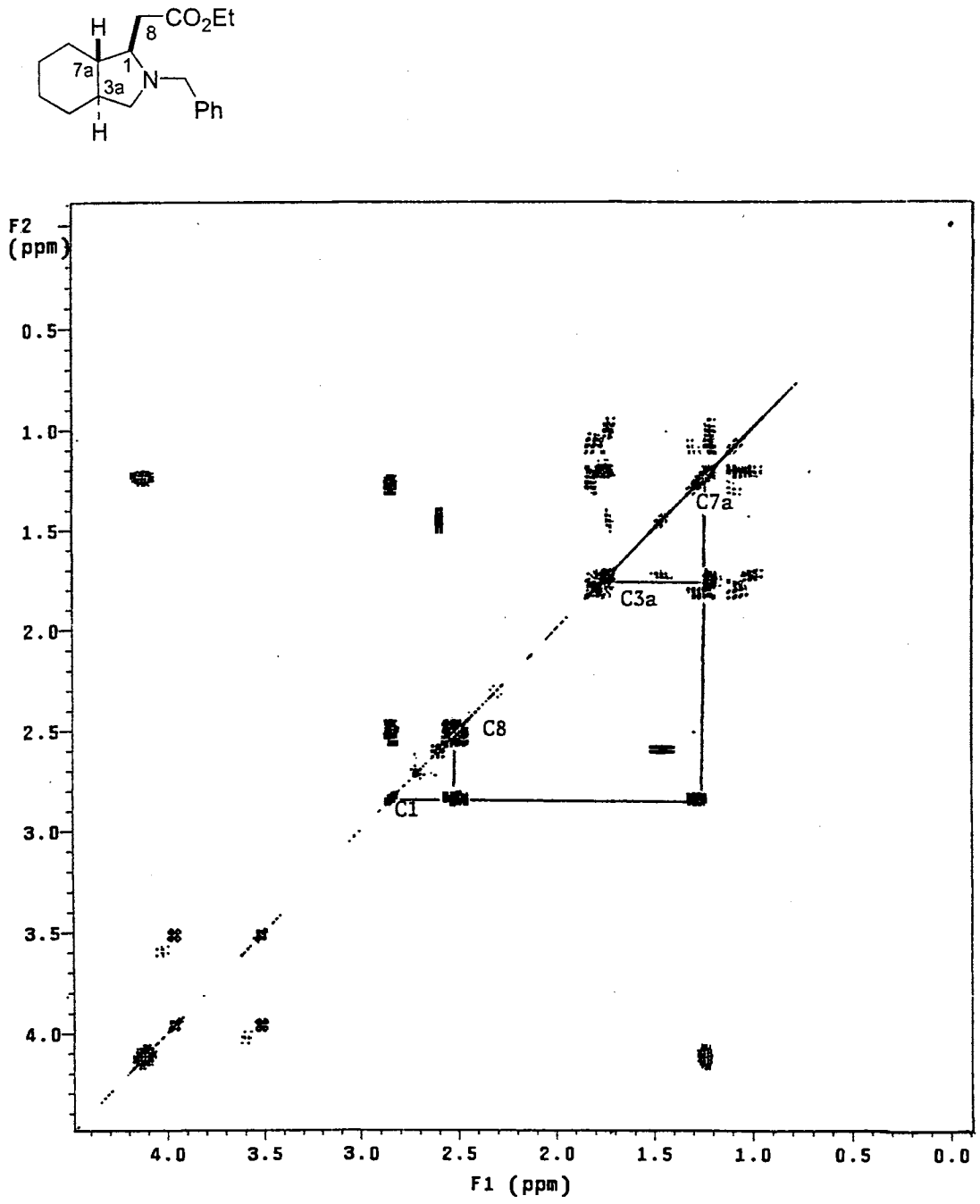
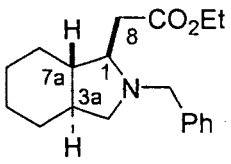


Plate V. COSY-45 of Ethyl (±)-(1*R**,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**31**)



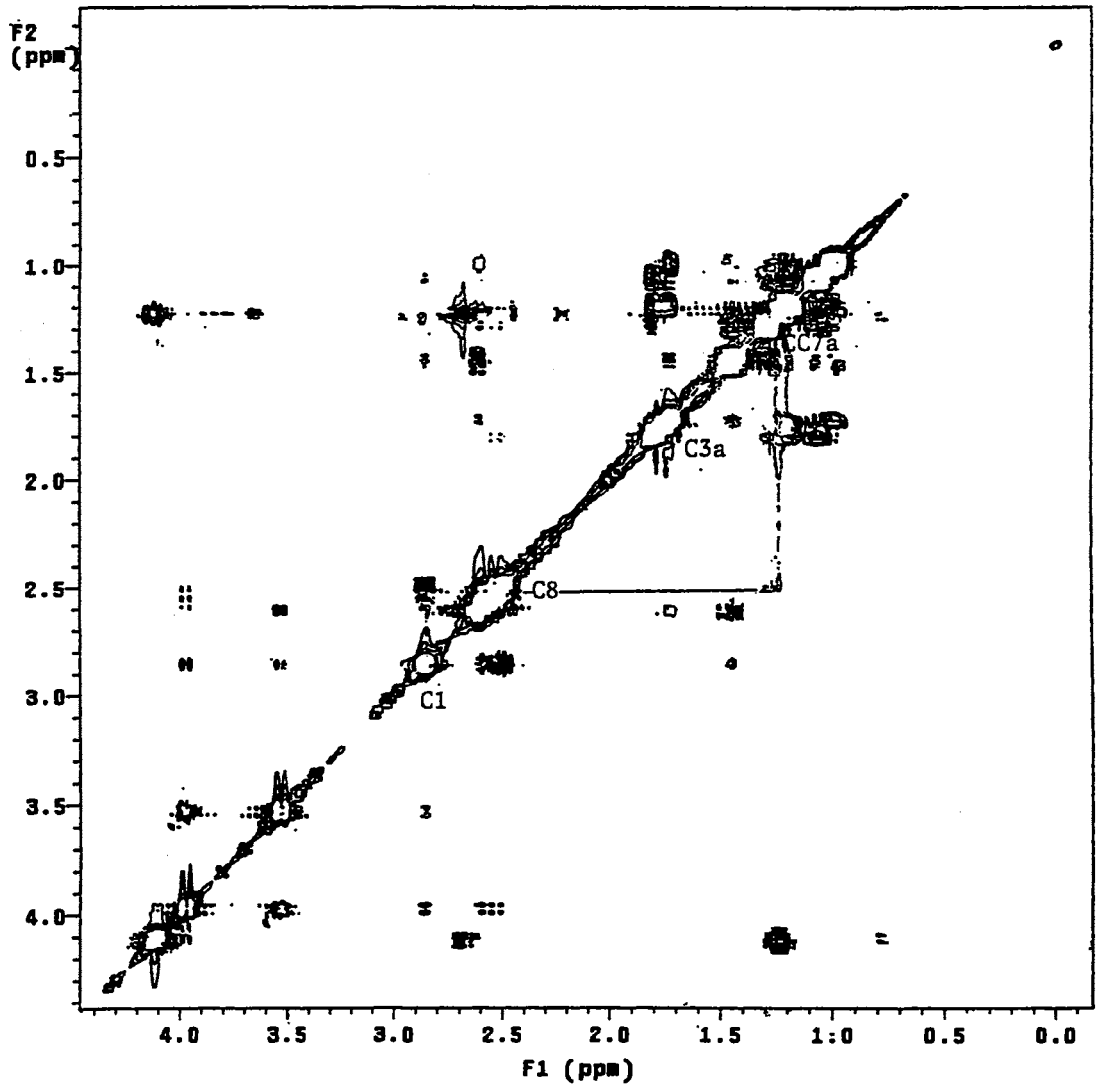
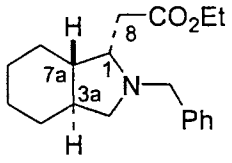


Plate VI. NOESY of Ethyl (±)-(1*R**,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**31**)



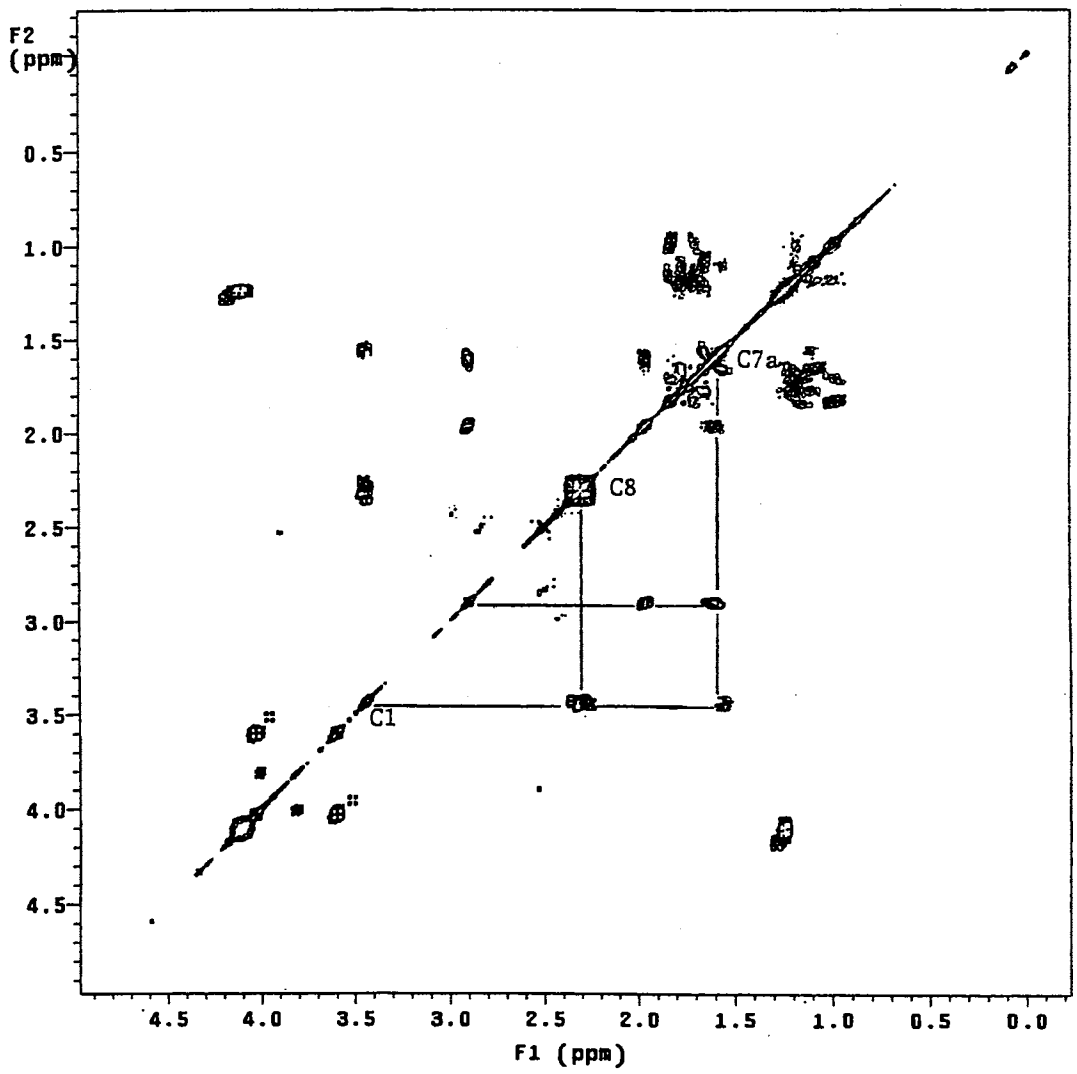


Plate VII. COSY-45 of Ethyl (±)-(1*S**,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**32**)

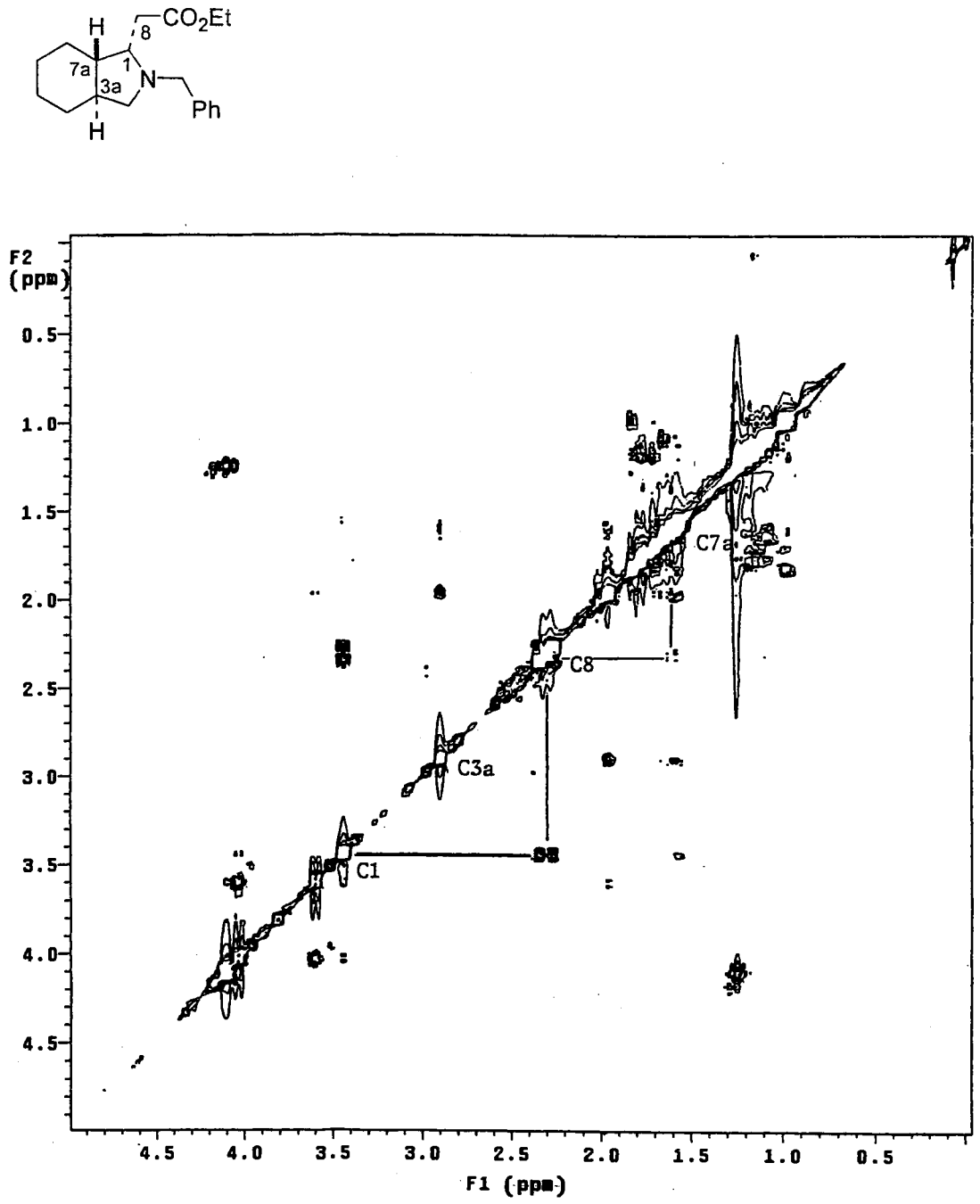


Plate VIII. NOESY of Ethyl (±)-(1*S**,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (**32**)

Mechanism of the ring closure for the nitrogen heterocycles. The heterocyclic ring closure reaction can occur in two ways: (1) The Michael Addition followed by the S_N2 reaction or (2) The S_N2 reaction followed by the Michael addition. The report of Bunce and co-workers,[44] however, suggests that the S_N2 displacement process is the initial step in the process. In view of this, the mechanism may be speculated to occur as shown in Figure 29. The reaction of the iodo ester proceeds with the primary amine through an S_N2 displacement of the halide by the lone pair of electrons on the primary nitrogen atom to yield a secondary aminium halide salt **34**, which then reacts with triethylamine to afford the secondary amine **35**. This amine then initiates an intramolecular Michael addition reaction with the acrylate acceptor to afford the cyclic product **36** (cis or trans).

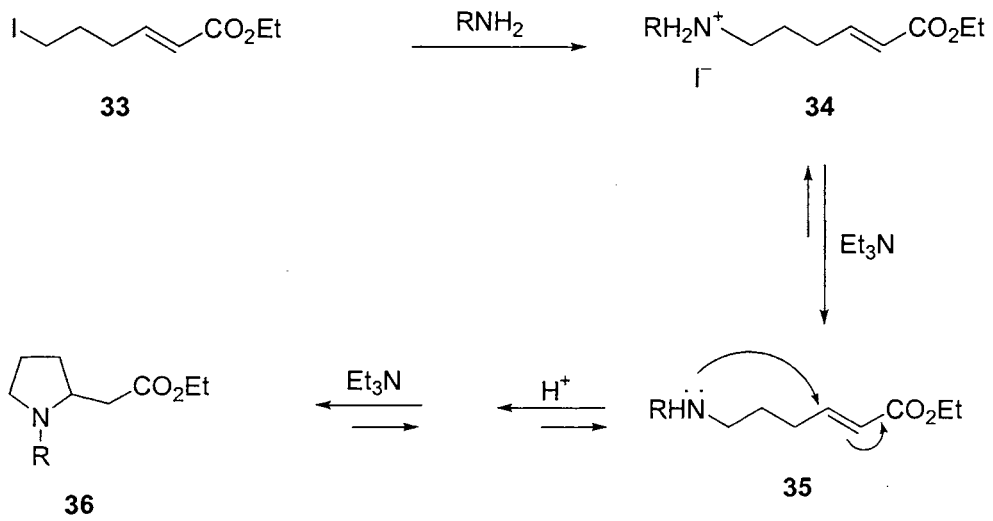


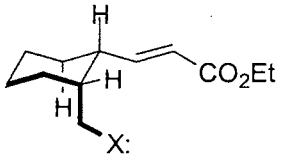
Figure 29. Mechanism of the formation of nitrogen heterocycles by a tandem S_N2 Michael addition sequence.

Several reports have suggested that closure of the cis substrate **12** should favor the all-cis product wherein the acetic acid side chain would be cis to the cis-oriented bridge head hydrogens.[45-48] The formation of the trans-fused system, however, has no precedent.

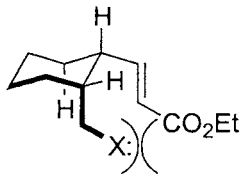
Previous syntheses of six-five fused carbocyclic systems using the Michael reaction involved closure of a cyclohexanone enolate on a side chain acceptor to form two new stereocenters α and β to the carbonyl. The reaction protocols for these cyclizations varied depending on the structure of the substrate but were invariably carried out under equilibrating conditions that led to the formation of the thermodynamic products. In each case, the all-cis six-five fused bicyclic structure was produced as the major product. This stereochemical outcome has been attributed to steric effects in the transition state.[45]

In this work, the stereochemistry of the ring junction is set prior to the ring closure and consequently cyclization creates only one new stereocenter at C1. Again, the reaction conditions should favor the thermodynamic products and steric factors should control the selectivity as shown in Figure 30.

Cis-fused

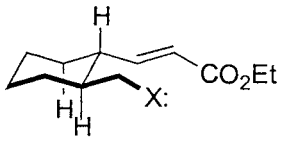


A: Major

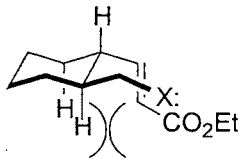


B: Minor

Trans-fused



A: Major



B: Minor

X: = $NHCH_2Ph$ or S^-

Figure 30. Possible rotamer states for the formation of products.

In leading to cis-fused product **29**, rotamer **A** would be preferred as it minimizes the 1,3-diaxial-like interaction between the Michael donor (CH_2-X:) and the acrylate acceptor present in rotamer **B**. Additionally, the cyclization of **B** forces the side chain into the molecular cavity created by the cis-fused rings and results in eclipsing of the side chain methylene with C7 of the octahydroisoindole. Thus, product **29** predominates over **30**. Likewise, for the trans-fused product **31**, a similar rotamer preference applies, although the steric differentiation is less pronounced. Furthermore, eclipsing of the side chain C7 is still present, but the two groups are not as close. Thus, the preference for product **31** over **32** is significantly reduced.

Preparation of six-five fused-ring bicyclic sulfur heterocycles. The method used to generate the six-five fused sulfur heterocycle from the cis iodo ester **12** is shown in Figure 31. The method proceeds by a two-step process involving 1) the reaction of the iodo ester **12** with thiourea in ethanol to afford the isothiuronium salt[49] **38** and 2) hydrolysis by aqueous base.[49] Hydrolysis results in release of the thiolate which undergoes Michael addition with the acrylate acceptor to afford the sulfur hetrocycle **39** as the carboxylic acid. The method used to generate the trans six-five fused sulfur heterocycle from the trans iodo ester **14** is shown in Figure 32.

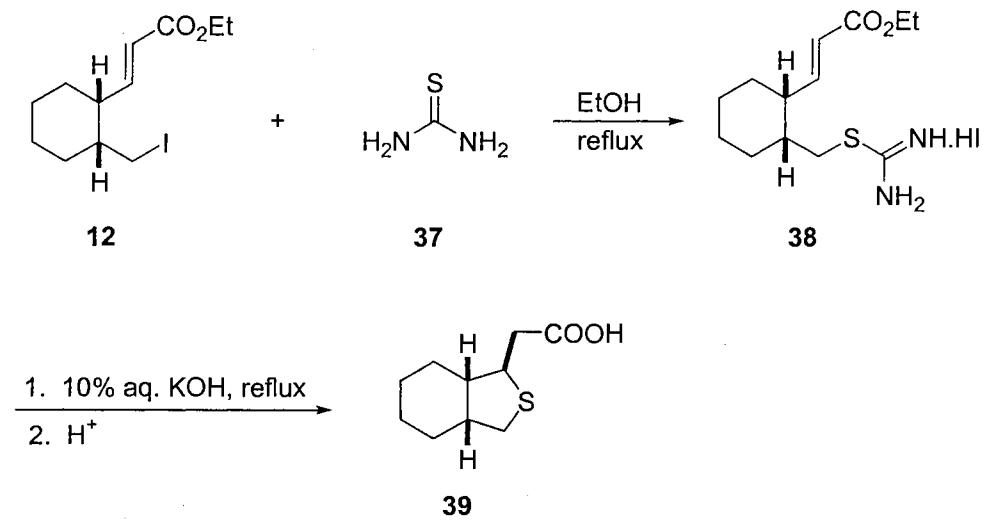


Figure 31. Synthesis of cis sulfur heterocycle **39** by a tandem S_N2-Michael addition sequence.

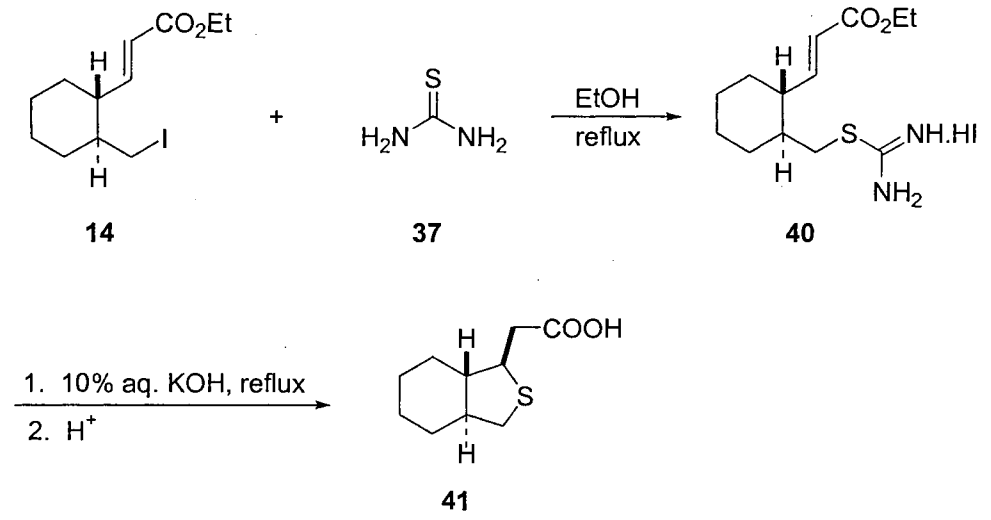


Figure 32. Synthesis of the trans sulfur heterocycle **41** by a tandem S_N2-Michael addition sequence.

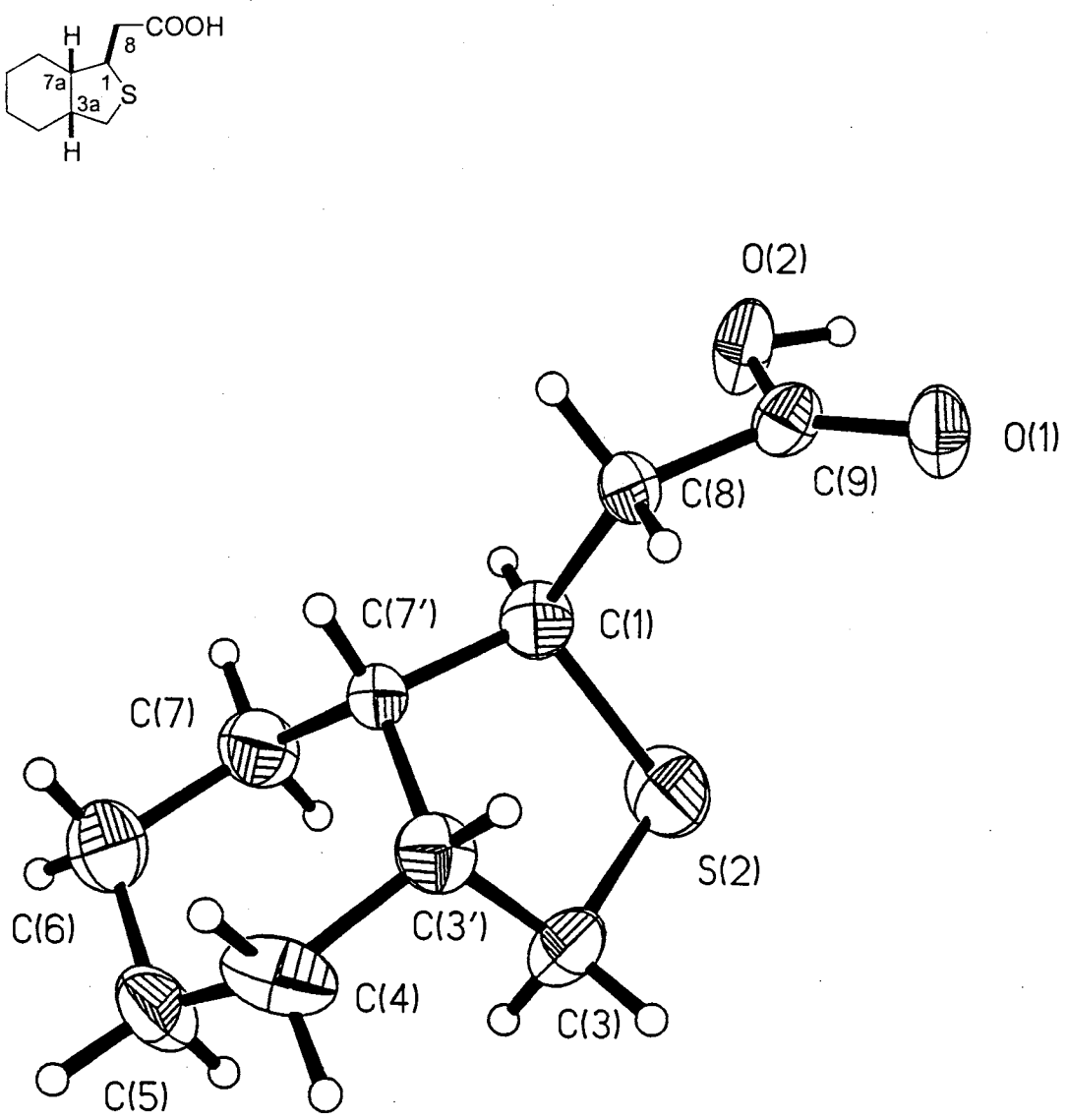


Plate IX. X-ray structure of (±)-(1*R**,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]-thiophene-1-acetic acid (**39**)

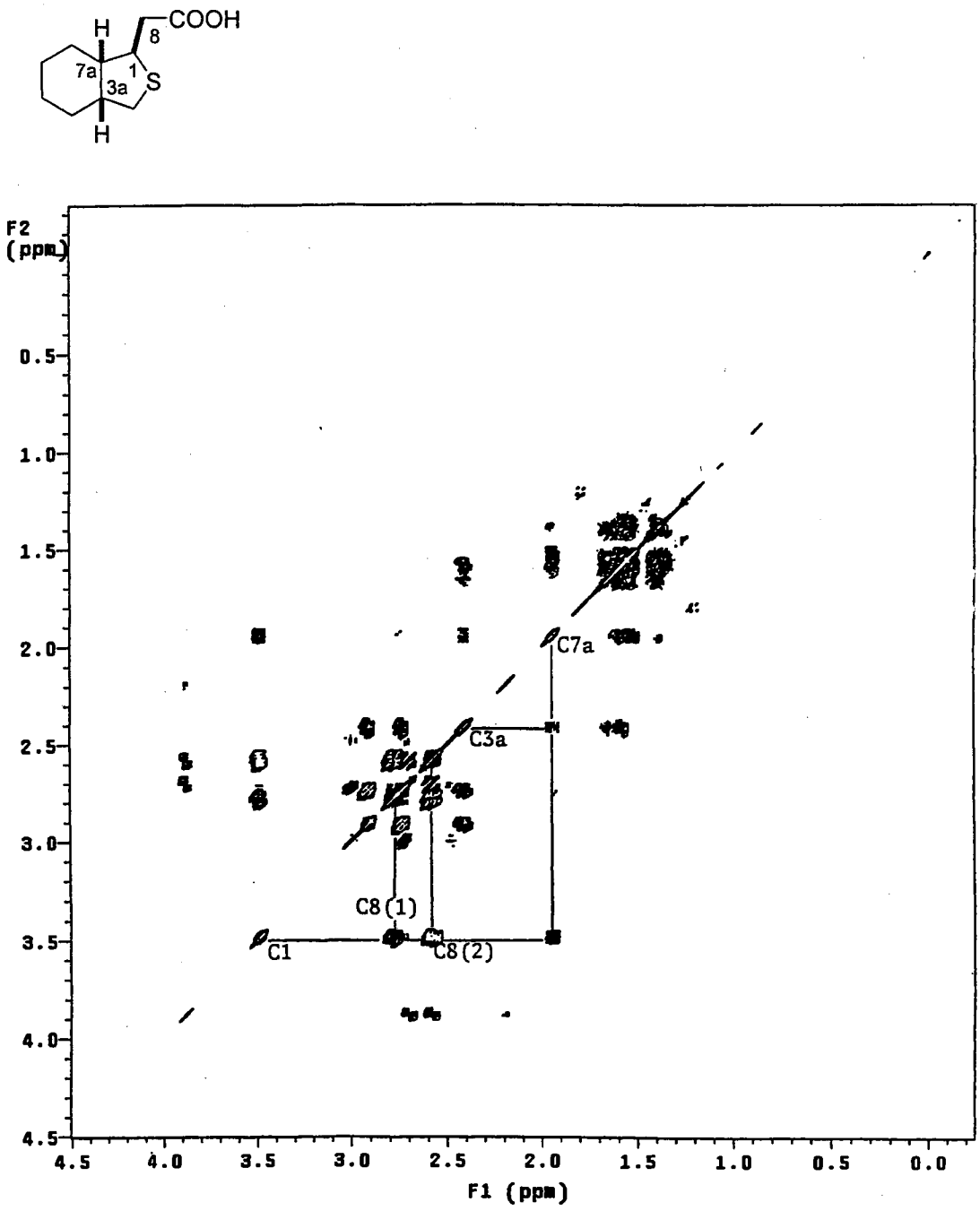


Plate X. COSY-45 of (±)-(1*R**,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]-thiophene-1-acetic acid (**39**)

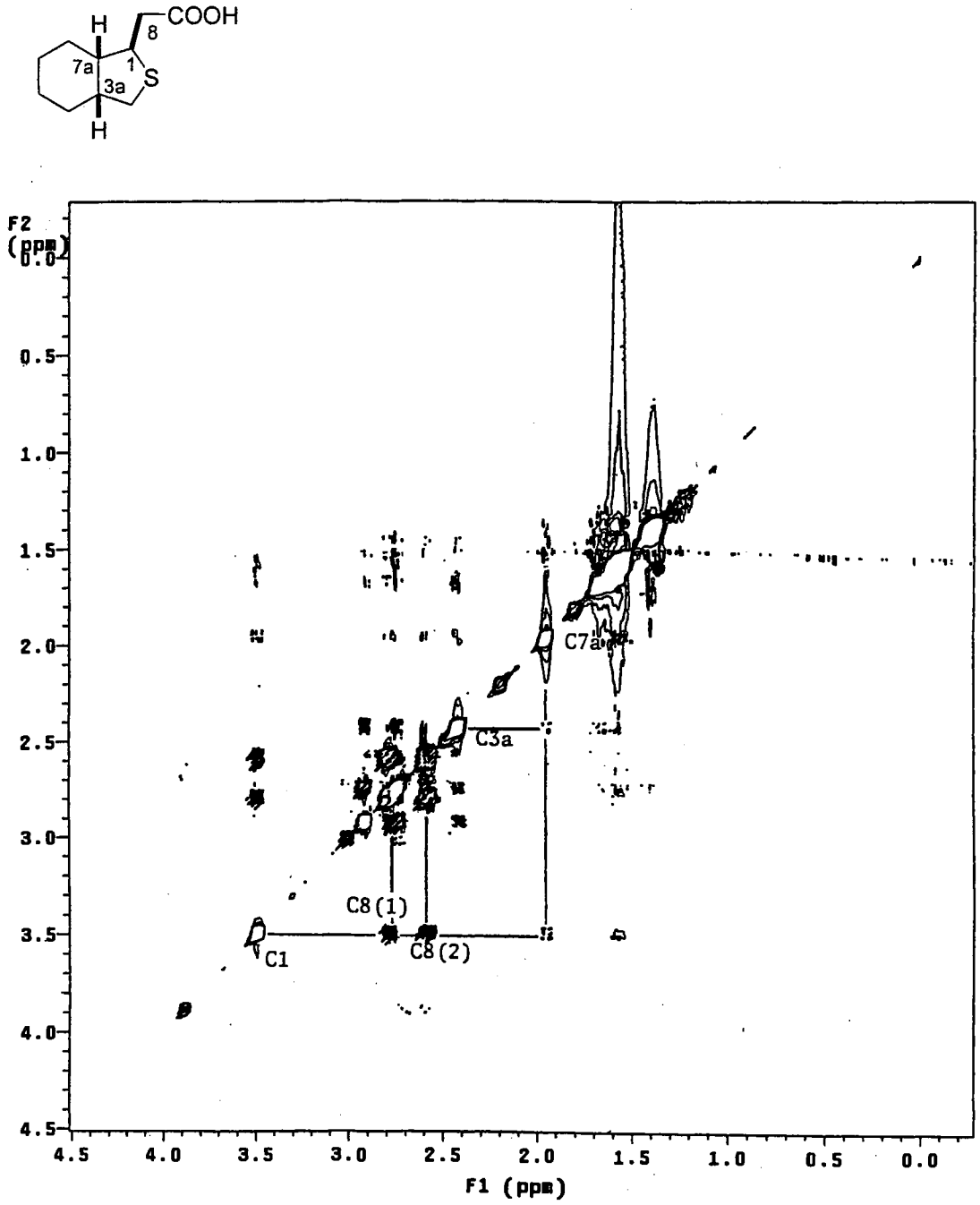
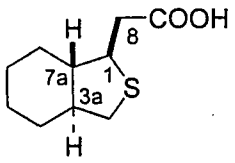


Plate XI. NOESY of (±)-(1*R**,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a-octahydrobenzo[*c*]-thiophene-1-acetic acid (**39**)



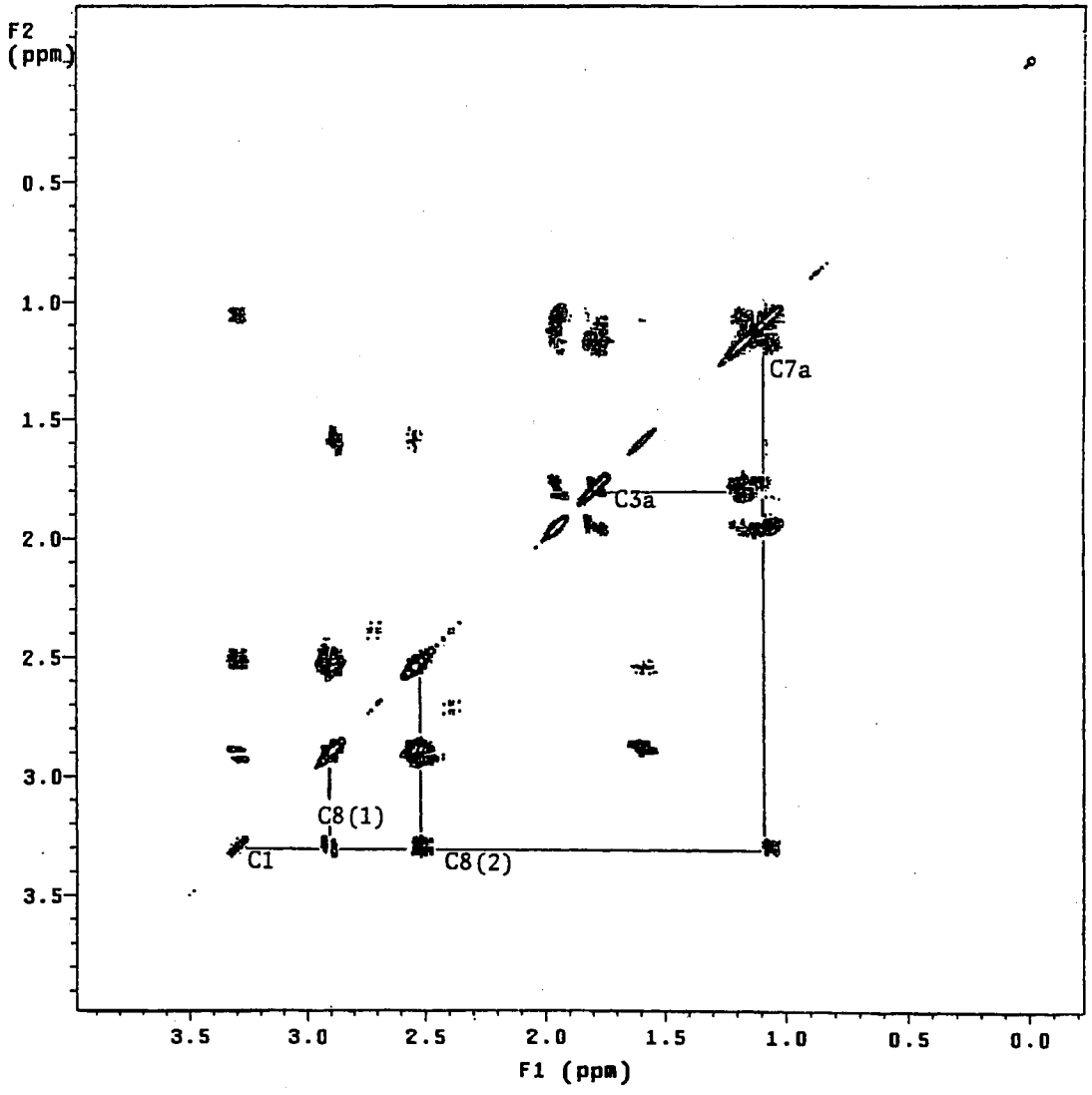


Plate XII. COSY-45 of (±)-(1*R**,3a*S**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]-thiophene-1-acetic acid (**41**)

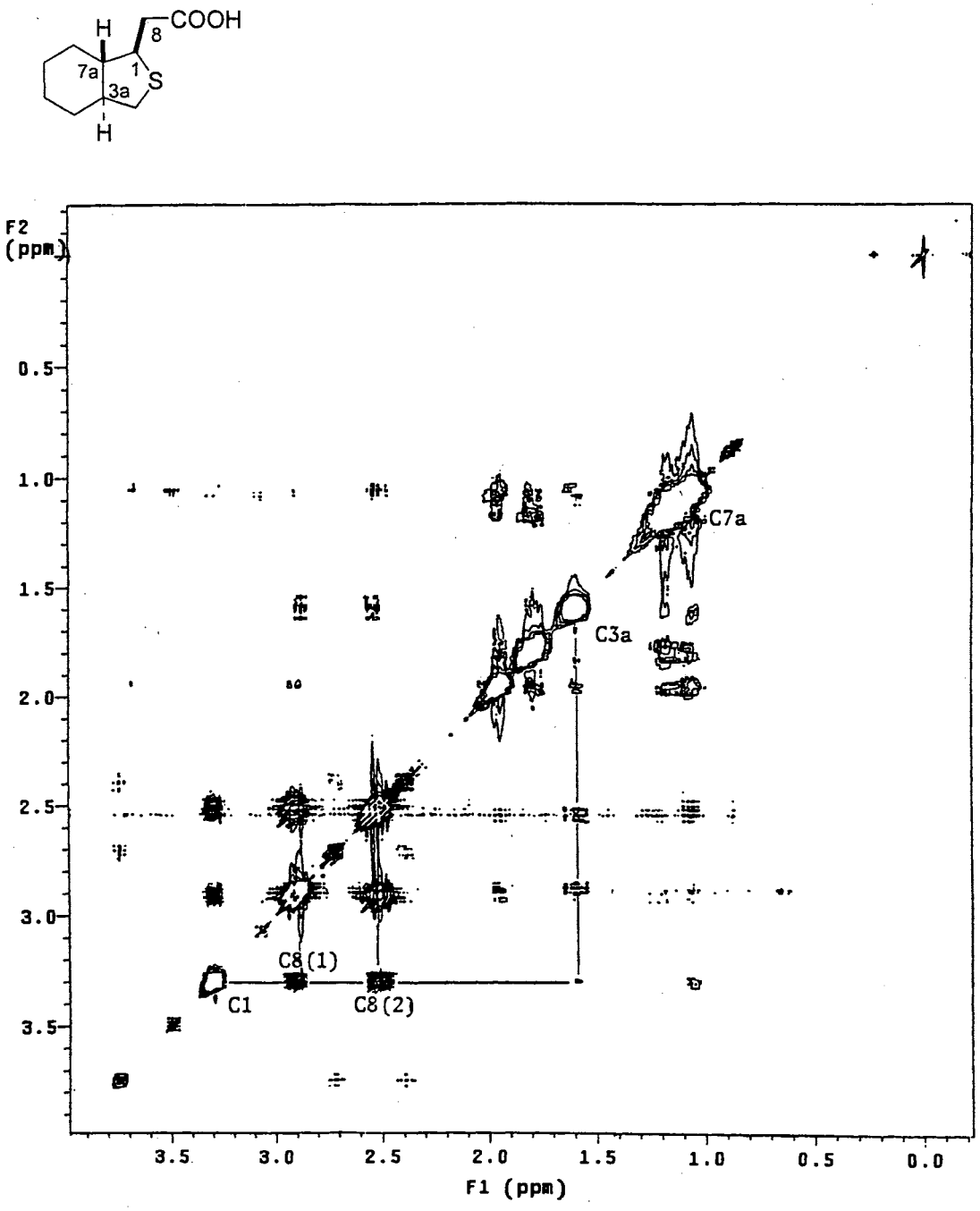


Plate XIII. NOESY of (±)-(1*R**,3a*S**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]-thiophene-1-acetic acid (41)

Mechanism of the ring closure for the sulfur heterocycles. The isolation of the isothiuronium salts **38** and **40** in the sulfur heterocyclization process makes the initial stages of the reaction less ambiguous. Clearly, the initial step is the displacement of the halide by an S_N2 reaction. The second step of the reaction can still proceed in two ways. The strong base used in the second step serves three purposes: (1) neutralization of the isothiuronium halide salt, (2) hydrolysis of the ester functional group, (3) cleavage of the amidine functional group to yield the free thiolate anion, which subsequently closes onto the Michael acceptor moiety. In view of this, the mechanism of ring closure for the sulfur heterocycles can be formulated to be as follows.

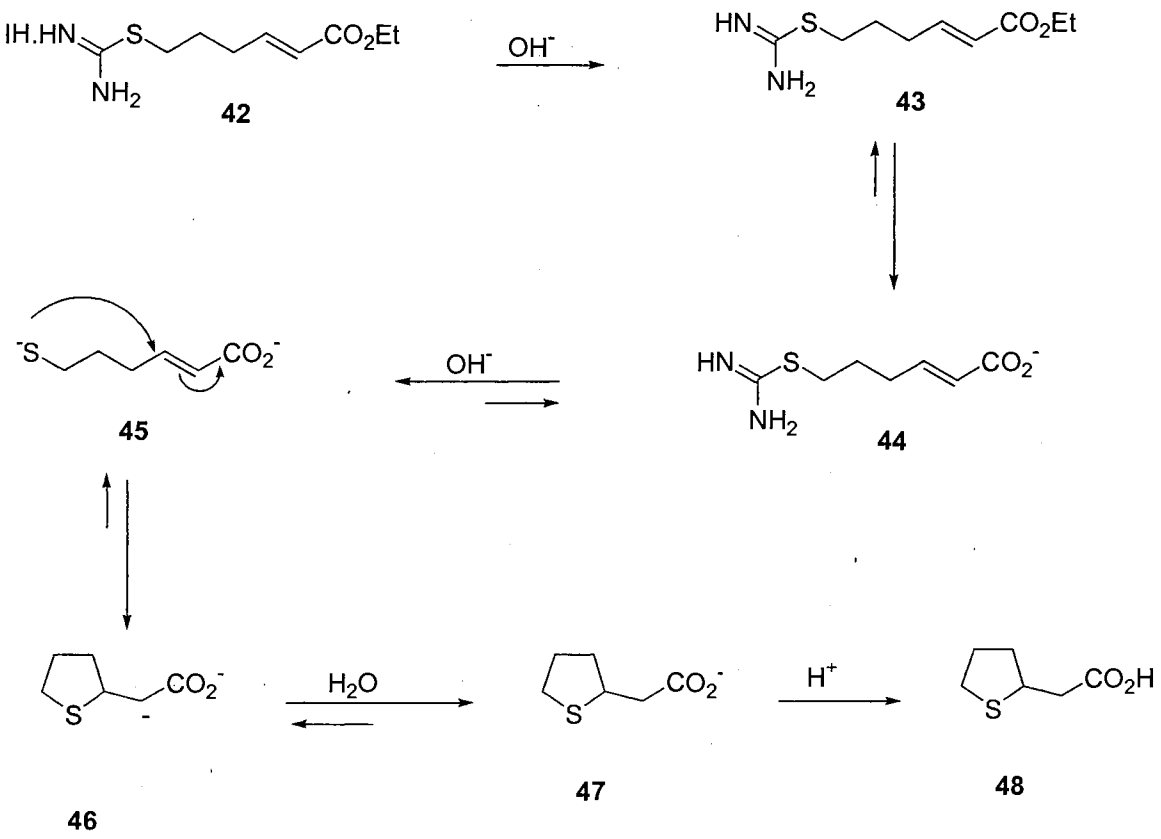


Figure 33. Mechanism of the formation of sulfur heterocycles by a tandem S_N2-Michael addition sequence.

Neutralization of the isothiuronium iodide salt **42** with the hydroxide ion initially yields the amidine intermediate **43**. This species then undergoes base hydrolysis of the ester functionality to afford the carboxylate **44**. Subsequent base hydrolysis of the amidine group then generates dianion **45** which cyclizes by Michael addition of the thiolate to the acrylic acid moiety to yield the carboxylate dianion **46**.[54] Protonation of the dianion by water affords the carboxylate intermediate **47**. Finally, acid workup gives the observed cyclic product **48**.

Conclusions. The S_N2-Michael Addition sequence demonstrates a viable methodology for the synthesis of saturated fused-ring systems in fairly good yields. This sequence provides an efficient approach for the construction of heterocyclic ring systems with specific stereochemical requirements. Furthermore, this process can be explored for the preparation of other polycyclic ring systems.

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Experimental Section

All solvents were distilled prior to use; other reagents were used as received from the vendors. All reactions were run under dry N_2 in oven-dried glassware. The 1 *M* HCl, 9 *M* H_2SO_4, 5% $Na_2S_2O_3$, saturated $NaHCO_3$ and saturated NaCl used in various procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard layer silica gel GF plates (Analtech) using UV or phosphomolybdic acid detection or (2) capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-300 °C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech) or (2) flash column chromatography on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies no. 5). In each case, band elution was monitored by using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. Unless otherwise noted, ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$; coupling constants (*J*) have been given in Hz. COSY-45 and NOESY spectra were recorded at 400 MHz. High-resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

(±)-(1*R,2S*)-1,2-Cyclohexanedimethanol (17).** The general procedure of Photis and Paquette[38] was followed. To a stirred slurry of 1.48 g (38.9 mmol) of $LiAlH_4$ in 150 mL of dry THF was added a solution of 5.00 g (32.5 mmol) of **16** in 30 mL of dry THF over the course of 15 min, and the resulting mixture was heated under reflux for 3 h. The reaction was then cooled to 0-5 °C, and 20 mL of a freshly prepared solution of saturated

Na_2SO_4 was added dropwise with stirring and cooling. Insoluble aluminum salts were removed by suction filtration through a 20 cm x 12 cm plug of Celite and was washed with several hot portions of THF. The collected filtrate was dried ($MgSO_4$) and concentrated to give 4.40 g (30.6 mmol, 94%) of **17** as a colorless thick oil, which was used without further purification. IR 3600-3000, 1030 cm^{-1}; ^1H NMR δ 4.32 (br s, 2 H), 3.58 (m, 2 H), 3.46 (m, 2 H), 1.70 (m, 2 H), 1.58 (m, 2 H), 1.25 (m, 4 H), 1.00 (m, 2 H); ^{13}C NMR δ 67.7, 44.7, 29.8, 26.1

(±)-(1*S,2*S**)-4-Cyclohexene-1,2-diethylcarboxylate (23).** The procedure of Sample and Hatch[41] was followed. A mixture of 15.0 g (127 mmol) butadiene sulfone (**21**), 1-2 crystals of hydroquinone, 14.6 g (84.6 mmol) diethyl fumarate (**22**) and 50 mL of toluene was placed in a pressure vessel, sealed, and heated at 110-115 °C for 36 h. Upon cooling to room temperature, the reaction mixture was poured into an Erlenmeyer flask, and the contents were vigorously stirred with a saturated solution of Na_2CO_3 for 10 min. The aqueous layer was separated and extracted with petroleum ether (2x). The combined organic layers were collected, washed with 20 mL of 5% cold Na_2CO_3 (2x), 20 mL of H_2O (2x), then dried ($MgSO_4$) and concentrated. Vacuum distillation afforded 22.9 g of **23** (101 mmol, 80%), bp 78-82 °C (0.5 mm); IR: 1737 cm^{-1}; ^1H NMR δ 5.69 (d, 2 H, J = 3.2 Hz), 4.14 (dq, 4 H, J = 5.4, 1.9 Hz), 2.87-2.81 (m, 4 H), 2.46- 2.44 (m, 1 H), 2.41-2.38 (m, 1 H), 2.21-2.13 (m, 4 H), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 174.8, 124.9, 60.6, 41.3, 27.9, 14.1.

(±)(1*S,2*S**)-Cyclohexane-1,2-diethylcarboxylate (24).** A 21.89 g (96.86 mmol) solution of **23** in EtOH was hydrogenated over 5% Pd/C for 2 h. Filtration of the reaction mixture through Celite, and concentration under vacuum yielded 21.83 g of **24** (95.74

mmol, 98.9%). IR 1744 cm^{-1}; ^1H NMR δ 4.12 (dq, 4 H, J = 3.6, 2.5 Hz), 2.6-2.56 (m, 2 H), 2.09-2.04 (m, 2 H), 1.8-1.6 (m, 2 H), 1.4-1.2 (complex); ^{13}C NMR δ 175.3, 60.7, 45.2, 29.2, 25.5, 14.4.

(±)(1*S,2*S**)-Cyclohexane-1,2-dimethanol (25)**. A 20.0 g (87.7 mmol) solution of **24** in 150 mL of freshly distilled dry anhydrous THF was added dropwise to a stirred suspension of 4.0 g (105.4 mmol) of $LiAlH_4$ in 50 mL of dry ether. The reaction was refluxed gently for 20 h. The contents were cooled to 25 °C and saturated Na_2SO_4 solution was added dropwise with stirring and cooling. The contents were filtered through Celite, and the residue was washed with several portions of hot ether. The filtrate was dried ($MgSO_4$) and concentrated to afford a white solid, which was recrystallized from ether-hexane to yield 12.1 g (84.0 mmol, 95.8 %) of **25**. IR 3640-3030, 1050 cm^{-1}; ^1H NMR δ 4.32 (br s, 2 H), 3.58 (m, 2 H), 3.46 (m, 2 H), 1.70 (m, 2 H), 1.58 (m, 2 H), 1.25 (m, 4 H), 1.00 (m, 2 H); ^{13}C NMR δ 67.8, 44.6, 29.8, 26.1.

1-Hydroxy-1,2-benziodoxol-3(*H*)-one-1-oxide (IBX). The procedure of Corey and Palani[39] was followed. Although IBX is known to be heat and impact sensitive, no problems were encountered under the reaction conditions followed here. To a vigorously stirred mixture of 3.74 g (15.1 mmol) of 2-iodobenzoic acid and 10 mL of 0.73 M H_2SO_4 maintained at 55 °C was added 3.35 g (19.9 mmol) of $KBrO_3$ over 0.5 h. After the addition was complete, the mixture was stirred for 3.5 h at 68 °C and then cooled in an ice bath. Filtration and washing of the solid with 5 mL of water and 2 x 10 mL of EtOH gave 3.74 g (13.46 mmol, 88.6%) of IBX.

Representative Procedure for the Synthesis of Lactols: (±)-(1a*S, 6a*S**)-7-Hydroxy-8-oxabicyclo[4.3.0]nonane (18)**. The procedure of Corey and Palani[39] was

followed. To a stirred solution of 2 mL of DMSO and 3.60 g (12.9 mmol) *o*-iodoxybenzoic acid, was added 1.50 g (10.4 mmol) **17**. The paste was stirred for 2 h at 23 °C and then quenched with 5 mL of H_2O. The mixture was filtered through Celite, and the filtercake was washed with H_2O and CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with 10 mL of CH_2Cl_2 (2x). The combined organic phase was dried ($MgSO_4$) and concentrated to afford 1.20 g (8.45 mmol, 81%) of **18**, which was used without further purification. IR 3560-3100, 2660, 1760 cm^{-1}; ^1H NMR δ 5.16 (m, 1 H), 4.23 (br s, 1 H), 3.72 (m, 2 H), 2.53 (m, 1 H), 2.05 (m, 1 H), 1.57-1.36 (complex, 8 H); ^{13}C NMR δ 102.5, 70.5, 44.9, 35.1, 24.7, 24.2, 23.3, 21.9.

(±)-(1a*S,6a*R**)-7-Hydroxy-8-oxabicyclo[4.3.0]nonane (26)**. This compound was prepared from **25** by the same procedure as **18**. IR 3550-3100, 1700 cm^{-1}; ^1H NMR and ^{13}C NMR showed all three expected open and closed isomeric forms of the lactol.

Representative Procedure for the Synthesis of Hydroxyesters 19 and 27 from lactols 18 and 26. A 50 mL benzene solution of 4.80 g (33.8 mmol) of **18** and 17.4 g (50.0 mmol) of ethyl (triphenylphosphoranylidene)acetate in 50 mL of benzene was refluxed for 16 h with stirring. The mixture was cooled to 25 °C and concentrated under vacuum to afford a brown semisolid mass. This mass was layered onto a 20 cm x 12 cm plug of silica gel in a sintered glass funnel[55] and 2.0 L of hexane:ether (75:25) was poured on the sample under aspirator vacuum. Concentration of the collected eluent afforded a viscous yellow oil, which was purified by flash chromatography using increasing the concentrations of ether in hexane. The physical and spectral properties of the products were as follows:

Ethyl (±)-(2*E*)-3-[(1*R,2*R**)-2-(Hydroxymethyl)cyclohexyl]-2-propenoate(19).** The third and largest band eluted with 22% ether in hexane, afforded 3.44 g (16.2 mmol, 48%) of **19** as a clear colorless thick oil after concentration. IR 3580-3140, 1723, 1652 cm^{-1}; ^1H NMR δ 7.16 (dd, 1 H, J = 15.6, 7.2 Hz), 5.88 (d, 1 H, J = 15.6 Hz), 4.19 (q, 2 H, J = 6.9 Hz), 3.45 (d, 1 H, J = 7.3 Hz), 2.67 (m, 1 H), 1.84 (m, 1 H), 1.73 (m, 1 H), 1.70-1.43 (complex, 6 H), 1.38 (m, 2 H), 1.26 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 166.8, 149.7, 121.6, 64.4, 60.1, 42.3, 39.1, 30.1, 24.9, 24.6, 22.1, 14.0. HRMS *m/z* calcd. for $C_{12}H_{20}O_3$: 212.1412; Found: 212.1418.

Anal. Calcd. For $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.77; H, 9.40.

Ethyl (±)-(2*E*)-3-[(1*R,2*S**)-2-(Hydroxymethyl)cyclohexyl]-2-propenoate (27).** Compound **27** was obtained in 3.38 g (16.0 mmol, 47%) as a clear colorless thick oil after concentration. IR 3580-3140, 1715, 1650 cm^{-1}; ^1H NMR δ 6.81 (dd, 1 H, J = 15.6, 7.2 Hz), 5.79 (d, 1 H, J = 15.6 Hz), 4.15 (q, 2 H, J = 6.9 Hz), 3.54 (d, 1 H, J = 10.9, 3.8 Hz), 3.42 (dd, 1 H, J = 10.9, 6.2 Hz), 2.02 (m, 1 H), 1.95-1.50 (complex, 6 H), 1.43-1.25 (complex, 4 H), 1.26 (t, 3 H, J = 6.9 Hz); ^{13}C NMR δ 166.8, 153.0, 120.8, 66.1, 60.3, 43.9, 43.2, 32.4, 28.8, 25.6, 25.4, 14.3. HRMS *m/z* calcd. for $C_{12}H_{20}O_3$: 212.1412; Found: 212.1415.

Anal. Calcd. For $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.84; H, 9.38.

Representative Procedure for the Synthesis of Methanesulfonate Esters 20 and 28 from Hydroxy Esters 19 and 27. The general procedure of Crossland and Servis[40] was followed. To a stirred solution of 1.84 g (8.68 mmol) of **19** and 1.32 g (1.81 mL, 13 mmol) of TEA in 30 mL of CH_2Cl_2 at 0-5 °C was added 1.20 g (0.81 mL, 10.4 mmol) of methanesulfonyl chloride dropwise over the course of 10 min. The resulting mixture was

stirred for 30 min with continued cooling. The mixture was poured into a 125 mL separatory funnel and extracted 10 mL of with ice water, 2 mL of 1.0 *M* HCl, 4 mL of $NaHCO_3$ and 10 mL of NaCl solutions, then dried ($MgSO_4$) and concentrated to afford **20** as a light yellow to orange oil, which was used for the next step without any further purification.

Ethyl (±)-(2*E*)-3-{(1*R,2*R**)-2-[(Methanesulfonyloxy)methyl]cyclohexane}-2-propenoate (20)**. This compound was obtained in 2.30 g (7.90 mmol, 91%) as an oil. IR 1720, 1655, 1360, 1175 cm^{-1}; ^1H NMR δ 7.10 (dd, 1 H, J = 15.6, 6.9 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.20 (q, 2 H, J = 7.2 Hz), 3.99 (m, 2 H), 2.99 (s, 3 H), 2.69 (m, 1 H), 2.04 (m, 1 H), 1.76 (m, 1 H), 1.65 (m, 2 H), 1.57 (m, 3 H), 1.41 (m, 2H), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 166.2, 147.7, 122.8, 71.4, 60.3, 39.4, 37.1, 29.9, 24.6, 21.7, 14.2. MS (chemical ionization, isobutene) *m/z* 291 (M^++1,39).

Ethyl (±)-(2*E*)-3-{(1*R,2*S**)-2-[(Methanesulfonyloxy)methyl]cyclohexane}-2-propenoate (28)**. This compound was obtained in 2.51 g (8.62 mmol, 98.4%) as an oil. IR 1710, 1650, 1365, 1175 cm^{-1}; ^1H NMR δ 6.77 (dd, 1 H, J = 15.6, 9.6 Hz), 5.82 (d, 1 H, J = 15.6 Hz), 4.16 (q, 2 H, J = 7.2 Hz), 4.09 (dd, 1 H, J = 9.6, 3.7 Hz), 3.97 (dd, 1 H, J = 9.6, 6.2 Hz), 2.95 (s, 3 H), 2.04 (m, 1 H), 1.95 (m, 1 H), 1.87-1.55 (complex, 4 H), 1.39-1.19 (complex, 4 H), 1.26 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 166.4, 151.0, 121.8, 72.7, 60.4, 42.9, 40.9, 37.1, 32.3, 28.5, 25.2, 25.1, 14.2. MS (chemical ionization, isobutene) *m/z* 291 (M^++1,100).

Representative Procedure for the Synthesis of Alkyl Iodides 12 and 14 from methanesulfonate esters 20 and 28. To a stirred solution of 0.68 g (2.34 mmol) of **20** in 10 mL of acetone was added 1.74 g (11.6 mmol) of NaI, and the mixture was refluxed for

14 h. The reaction mixture was cooled to 25 °C and concentrated under vacuum to afford a solid orange residue. The residue was dissolved in 15 mL of H_2O and extracted with ether (2x). The combined ether extracts were washed with H_2O, 5% $Na_2S_2O_3$, NaCl solutions, then dried ($MgSO_4$) and concentrated under vacuum to yield the iodo ester. The compounds were used directly for the next step without further purification.

Ethyl (±)-(2*E*)-3-[(1*R,2*R**)-2-(Iodomethyl)cyclohexyl]-2-propenoate (12).** This compound was obtained in 0.62 g (1.92 mmol, 82%) as an oil. IR 1730, 1650 cm^{-1}; ^1H NMR δ 7.02 (dd, 1 H, J = 15.6, 9.3 Hz), 5.97 (d, 1 H, J = 15.6 Hz), 4.20 (q, 2 H, J = 6.6 Hz), 3.08 (dd, 1 H, J = 9.8, 7.3 Hz), 2.93 (dd, 1 H, J = 9.8, 8.0 Hz), 2.78 (m, 1 H), 1.91 (m, 1 H), 1.78-1.55 (complex, 4 H), 1.52-1.26 (complex, 4 H), 1.30 (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 166.3, 147.5, 122.9, 60.2, 42.7, 41.3, 30.5, 24.9, 14.2. MS (chemical ionization, isobutene) *m/z* 323 (M^++1,68).

Ethyl (±)-(2*E*)-3-[(1*R,2*S**)-2-(Iodomethyl)cyclohexyl]-2-propenoate (14).** This compound was isolated in 0.63 g (1.96 mmol, 84%) as a colorless oil. IR: 1730 cm^{-1}; ^1H NMR δ 6.70 (dd, 1, H, J = 9.7, 9.7 Hz), 5.93 (d, 1 H, J = 15.7 Hz), 4.19 (q, 2 H, J = 7.0 Hz), 3.28 (m, 1 H), 3.06 (m, 1 H), 2.03 (m, 2 H), 1.86-1.22 (complex, 5 H), 1.19 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 166.5, 151.2, 121.8, 60.2, 45.8, 41.3, 32.2, 30.5, 25.3, 16.0, 14.2. MS (chemical ionization, isobutene) *m/z* 323 (M^++1,100).

Representative Procedure of the Synthesis of Heterocycles 29 and 30. A 5 mL solution of 356 mg (1.11 mmol) of **12**, 132 mg (0.13 mL, 1.21 mmol) of benzylamine and 111 mg (0.15 mL, 1.23 mmol) of TEA in EtOH was stirred under reflux for 120 h. The reaction was cooled and concentrated under vacuum to afford a reddish-yellow oil, which was treated with 20 mL of H_2O and extracted with ether (2x). The ether extracts were

washed with H_2O, 5% aqueous $Na_2S_2O_3$, saturated NaCl, then dried ($MgSO_4$) and concentrated under vacuum to yield a light yellow oil which was purified by PTLC. The elution sequence was hexane (2x), 99:1 hexane:ether (2x), 95:5 hexane:ether (2x), 90:10 hexane:ether (2x), 85:15 hexane:ether (1x). The third band afforded **30** as a clear colorless oil. The fourth and largest band yielded **29** as a light yellow oil.

Ethyl (±)-(1*R,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (29)**. This compound was obtained in 268 mg (0.89 mmol, 80%) as an oil. IR (thin film) 1734 cm^{-1}; ^1H NMR δ 7.26 (m, 5 H), 4.12 (q, 2 H, J = 7.2 Hz), 4.02 (d, 1 H, J = 13.2 Hz), 3.59 (d, 1 H, J = 13.2 Hz), 2.98 (m, 1 H), 2.80 (m, 1 H), 2.45 (m, 2 H), 2.30 (m, 2 H), 1.82 (m, 1 H), 1.58 (m, 4 H), 1.35 (m, 4 H), 1.24 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 172.7, 140.8, 128.6, 128.1, 126.7, 66.7, 60.6, 60.2, 56.0, 43.7, 41.3, 35.8, 28.4, 25.7, 24.6, 22.5, 14.3; HRMS *m/z* calcd for $C_{19}H_{27}NO_2$: 301.2036, found, 301.2035.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.64; H, 9.07; N, 4.77.

Ethyl (±)-(1*S,3a*R**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (30)**. This compound was obtained in 18 mg (0.06 mmol, 5%) as an oil. IR 1730 cm^{-1}; ^1H NMR δ 7.26 (m, 5 H), 4.13 (q, 2 H, J = 7.6 Hz), 3.92 (d, 1 H, J = 13.8 Hz), 3.41 (d, 1 H, J = 13.8 Hz), 3.21 (m, 1 H), 2.92 (m, 1 H), 2.49 (m, 2 H), 2.31 (m, 2 H), 2.02 (m, 1 H), 1.71(m, 1 H), 1.63-1.12 (complex, 7 H), 1.25 (t, 3 H, J = 7.6 Hz); ^{13}C NMR δ 172.9, 140.7, 128.3, 128.1, 126.6, 65.3, 60.2, 58.7, 54.8, 41.0, 35.4, 25.5, 24.8, 22.9, 20.9, 14.2; HRMS *m/z* calcd for $C_{19}H_{27}NO_2$: 301.2036, found, 301.2036.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.94; H, 9.18; N, 4.74.

Representative Procedure of the Synthesis of Heterocycles 31 and 32. Compound **14** (360 mg, 1.12 mmol) was reacted in the same manner as described for the synthesis of **29** and **30** from **12** and gave a mixture of **31** and **32**. Preparative TLC showed four bands. Bands 3 and 4 contained products **32** and **31**, respectively.

Ethyl (±)-(1*R,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (31).** The fourth and largest band yielded 236 mg (0.78 mmol, 70%) of **31** as a light yellow oil. IR 1730 cm^{-1}; ^1H NMR δ 7.27 (m, 5 H), 4.13 (q, 2 H, J = 7.2 Hz), 3.96 (d, 1 H, J = 13.8 Hz), 3.51 (d, 1 H, J = 13.8 Hz), 2.84 (m, 1 H), 2.60 (m, 2 H), 2.50 (m, 2 H), 1.84-1.72 (complex, 4 H), 1.46 (m, 1 H), 1.29 (m, 1 H), 1.24 (t, 3 H, J = 7.2 Hz), 1.22 (m, 1 H), 1.08 (m, 3 H); ^{13}C NMR δ 172.8, 128.5, 128.2, 126.6, 66.5, 60.2, 59.8, 57.3, 51.0, 43.0, 39.1, 29.3, 28.7, 25.9, 25.8, 14.2; MS (EI/DP): *m/z*, (%) 301 (11), 215 (17), 214 (100), 213 (9), 91 (38), 65 (3); HRMS *m/z* calcd for $C_{19}H_{27}NO_2$: 301.2036; found, 301.2034.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.50; H, 9.05; N, 4.73.

Ethyl (±)-(1*S,3a*S**,7a*S**)-*N*-Benzyl-2,3,3a,4,5,6,7,7a-octahydro-1*H*-isoindole-1-acetate (32).** The third band afforded 40 mg (0.13 mmol, 12%) of **32** as a clear light yellow oil. IR 1726 cm^{-1}; ^1H NMR δ 7.25 (m, 5 H), 4.11 (q, 2 H, J = 7.2 Hz), 4.04 (d, 1 H, J = 12.9 Hz), 3.61 (d, 1 H, J = 12.9 Hz), 3.45 (m, 1 H), 2.91 (m, 1 H), 2.32 (m, 2 H), 1.97 (m, 1 H), 1.87-1.46 (complex, 6 H), 1.25 (t, 3 H, J = 7.2 Hz), 1.27-0.98 (complex, 4 H); ^{13}C NMR δ 173.0, 140.1, 128.8, 128.1, 126.7, 62.5, 61.0, 60.2, 59.4, 47.5, 42.1, 39.0, 29.5, 26.6, 26.2, 25.7, 14.2; MS (EI/DP): *m/z*, (%) 301 (4), 215 (17), 214 (100), 91 (67), 65 (5); HRMS *m/z* calcd for $C_{19}H_{27}NO_2$: 301.2036; found, 301.2033.

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.75; H, 8.97; N, 4.65. Found: C, 75.61; H, 9.01; N, 4.68.

Representative Procedure for the Synthesis of Isothiuronium Adducts 38 and 40 from 12 and 14. The general procedure of Speziale[49] was followed. A 5 mL solution of 660 mg (2.05 mmol) of **12** in ethanol and 156 mg (2.05 mmol) of thiourea was refluxed with stirring for 120 h. The resulting mixture was cooled to 25 °C and concentrated to yield a white tacky solid which was used without further purification.

(±)-(1*S,2*S**)-1-(*E*)-2-Ethoxycarbonylethenyl-2-[(isothiuronium)methyl]cyclohexane iodide (38).** A tan solid weighing 800 mg (2.01 mmol, 98%) was isolated. IR 3540-2850, 1720, 1660, 1620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.07 (br s, 4 H), 7.02 (dd, 1 H, J = 15.6, 7.2 Hz), 5.93 (d, 1 H, J = 15.6 Hz), 4.13 (q, 2 H, J = 7.2 Hz), 3.00 (m, 2 H), 2.71 (m, 1 H), 1.84 (m, 1 H), 1.62 (m, 4 H), 1.37 (m, 4 H), 1.22 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 169.8, 165.5, 148.4, 122.5, 60.0, 40.1, 33.1, 29.1, 27.0 (2), 23.7, 21.7, 14.2. MS (FAB, thioglycerol): m/z 271 (M^+-I)

(±)-(1*R,2*S**)-1-(*E*)-2-Ethoxycarbonylethenyl-2-[(isothiuronium)methyl]cyclohexaneiodide (40).** This adduct was obtained in 790 mg (1.99 mmoles, 97%) as a light brown heavy oil. IR: 3650-2720, 1730, 1655, 1645 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.03 (br s, 4 H), 6.75 (dd, 1 H, J = 15.6, 6.9 Hz), 5.89 (d, 1 H, J = 15.6 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 3.19 (m, 1 H), 2.94 (m, 1 H), 2.07 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 4 H), 1.22 (t, 3 H, J = 7.2 Hz), 1.17 (m, 3 H), 1.10 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 170.0, 165.6, 151.5, 121.6, 59.8, 45.0, 39.7, 35.5, 31.7, 29.8, 24.9, 24.7, 14.2. MS (FAB, thioglycerol): m/z 271 (M^+-I)

Representative Procedure for the Synthesis of the Octahydrobenzo[*c*]thiophenes 39 and 41. The general procedure of Speziale[49] was followed. A mixture of 800 mg (2.01 mmoles) of **38** and 10 mL of 10% KOH in H_2O was refluxed with stirring for 36 h. The mixture was cooled to 25 °C and acidified at 0-5 °C by dropwise addition of concentrated H_2SO_4 to a pH of 2. The resulting mixture was extracted with ether (2x), washed with aqueous NaCl solution, then dried ($MgSO_4$), concentrated under vacuum and purified by recrystallization.

(±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]thiophene-1-aceticacid (39)**. Compound **39** was obtained as colorless needles in 280 mg (1.40 mmol, 69.7%), mp 83-84 °C from ether-hexane. IR: 1725 cm^{-1}; ^1H NMR δ 11.20-10.30 (br s, 1 H), 3.48 (m, 1 H), 2.89 (m, 1 H), 2.75 (m, 1 H), 2.52 (m, 1 H), 2.40 (m, 1 H), 1.92 (m, 1 H), 1.57 (m, 6 H), 1.37 (m, 2 H); ^{13}C NMR δ 177.9, 48.6, 46.3, 42.2, 42.1, 34.8, 26.5, 26.1, 23.2, 23.0; MS (EI/DP): *m/z* (%) 202 (M+2, 4), 200 (60), 166 (18), 154 (21), 141 (100), 135 (12), 121 (6), 107 (50), 93 (38), 79 (29), 67 (28); HRMS *m/z* calcd for $C_{10}H_{16}SO_2$: 200.0866; found, 200.0869.

Anal. Calcd. for $C_{10}H_{16}SO_2$: C, 60.00; H, 8.00. Found: C, 60.28; H, 8.05.

Structure elucidation of sulfur heterocycle 39. The *exo* stereochemistry of the acetate residue of the sulfur heterocycle **39** was assigned from a single crystal X-ray diffraction study of a crystal obtained from the crystals grown in ether-pentane. Intensity data were measured on a Brucker P4 diffractometer with MoK_α radiation (λ = 0.71073 Å) at room temperature.[50] All non-hydrogen positions were determined using SHELXS[51] structure solution program and refined by full matrix least squares methods on the basis of F^2 using the SHELX97[52] refinement program. Hydrogen atoms were placed in

calculated positions using idealized geometry and constrained to those positions during final refinements.

(±)-(1*R,3a*S**,7a*S**)-1,3,3a,4,5,6,7,7a-Octahydrobenzo[*c*]thiophene-1-acetic Acid (41)**. This compound was obtained as colorless needles from ether-hexane in 299 mg (1.50 mmol, 75%) with the following characteristics; mp 130-132 °C; IR: 3590-2870, 1720 cm^{-1}. ^1H NMR δ 3.29 (m, 1 H), 2.89 (m, 2 H), 2.52 (dd, 2 H, J = 9.9, 7.7 Hz), 1.94 (m, 2 H), 1.79 (m, 2 H), 1.59 (m, 1 H), 1.17 (m, 2 H), 1.06 (m, 3 H); ^{13}C NMR δ 177.9, 52.9, 48.6, 48.2, 39.9, 36.6, 31.8, 30.0, 25.5, 25.4; MS (EI/DP): *m/z* (%) 202 (M+2, 4), 200 (60), 166 (18), 154 (21), 141 (100), 135 (12), 121 (6), 107 (50), 93 (38), 79 (29), 67 (28); HRMS *m/z* calcd for $C_{10}H_{16}SO_2$: 200.0866; found, 200.0865.

Anal. Calcd. for $C_{10}H_{16}SO_2$: C, 60.00; H, 8.00. Found: C, 60.23; H, 8.02.

CHAPTER III

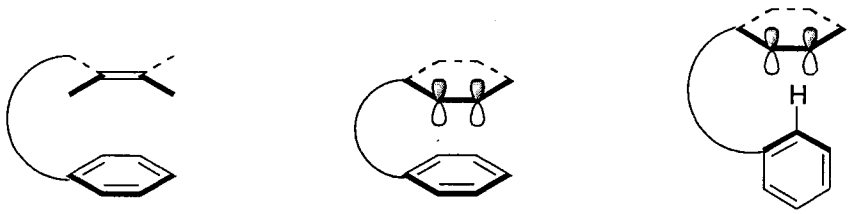
THE ROLE OF π-SHIELDING EFFECTS OF (-)-8-PHENYLMENTHOL IN ASYMMETRIC INDUCTION

INTRODUCTION

The term π-shielding, first coined by Corey in 1973,[56] over the years, has come to signify one face of an unsaturated moiety being shielded from the attack of an incoming species by an interaction with a pendant aryl group. The pendant aryl group in (-)-8-phenylmenthol serves to shield the α face of the unsaturated group on **1**. The exposed face can then be subjected to a variety of reaction conditions. The phenyl group serves as a stereodifferentiator, and thus imparts stereoselectivity.

In the present work, benzylic protons are abstracted using a base. This leads to the formation of an enolate. The formation of an enolate causes an interaction with the pendant phenyl group which can be of two kinds. 1) steric interactions, which serve to prevent the approach to the shielded face, and 2) electronic interactions, where a stabilizing interaction between the two components is established. When the intramolecular distance between the unsaturated group and the phenyl group is within the 3–5 Å range, both types of interactions are known to occur and are often referred to as π-stacking. Within this chapter all references to π-stacking are cases where an attractive

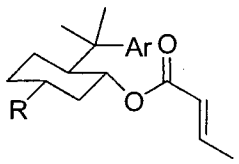
interaction between the unsaturated group and the phenyl ring exists. The π cloud of the unsaturated entity has either a face-to-face (**2**) or face-to-edge (**3**) relationship with the aryl group.



1 **2** **3**

Figure 34. π-Shielding effects in imparting stereoselectivity.

Corey and co-workers reported[56,57] the use of (-)-8-phenylmenthol as a chiral auxiliary, which became the first example of π-stacking and its application in organic synthesis for asymmetric induction. Further, acrylate esters of (-)-8-phenylmenthol have been shown[58] to have pronounced diastereoselectivity in intermolecular addition. Maddaluno and co-workers[59] carried out semi-empirical studies on crotonates **4** and have reported the contribution of π-stacking to diastereoselectivity in crotonates **4** (Ar = phenyl or 2-naphthyl) and suggested electrostatic forces were responsible for the interactions.



4

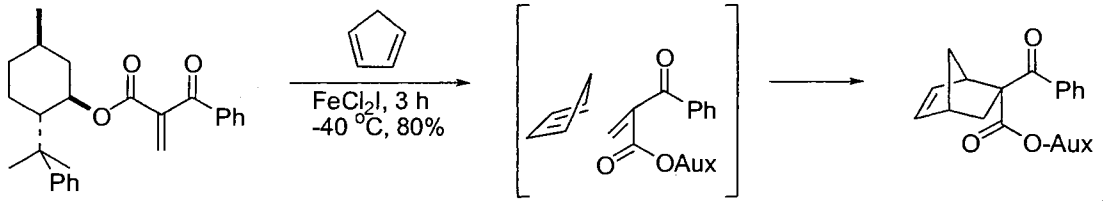
Figure 35. Stereodirecting effect of the aryl group in the crotonate **4**.

Simultaneously, Mezrhab and co-workers[60] independently reported the nature of the face-face interaction. This finding was supported by crystallographic analysis of **4**, which

revealed a coplanar relationship between the aryl and crotonate groups. This data agreed well with earlier fluorescence quenching studies, which suggested a through space π-π interaction.[58] The following reactions illustrate the role of (-)-8-phenylmenthol and its π-shielding effects in various types of reactions for asymmetric induction in modern organic synthesis.

Diels-Alder Reactions

Since its introduction in the 1970s, (-)-8-phenylmenthol has been used as a chiral auxiliary on the dienophile in the Diels-Alder cycloaddition.[56] It has also been used attached to a diene. The use of (-)-8-phenylmenthol as a chiral auxiliary for cycloadditions has been reported by Yamaguchi and co-workers.[61] The addition of cyclopentadiene to dienophile **5** is reported to have given adduct **7** as a single isomer. The approach of the diene indicated by **6** presumably shields the α face of the methylene effectively via the phenyl group of the auxiliary. The selectivity at room temperature was reported to afford a >99:1 ratio of adducts as shown in Figure 36.



5 **6** **7**

Figure 36. Cycloaddition to 2-methylene-1,3-dicarbonyl esters of (-)-8-phenylmenthol.

Aveneza and co-workers[62] reported that titanium-catalyzed addition of butadiene to **8** gave >99:1 of the cycloadduct with the *S* configuration at the new stereocenter. This was subsequently converted to bicyclo[3.3.1]derivative **10** on treatment with *N*-iodosuccinimide as shown in Figure 37.

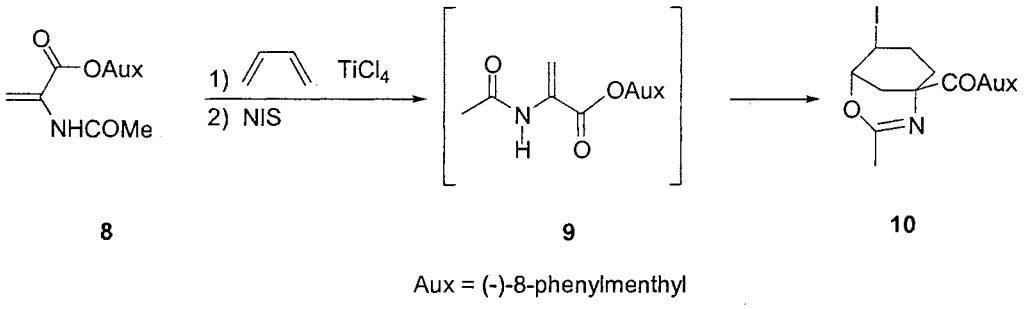


Figure 37. Cycloaddition of butadiene to (-)-8-phenylmenthyl acetamidoacrylates.

[2+2] Cycloadditions

The addition of dichloroketene **12** to (-)-8-phenylmenthol-derived enamide **11** was recorded by Correia and Miranda.[63] Product **14** was reported to have been formed with a high degree of stereocontrol. The authors have attributed the observed facial control on the basis of the transition state **13**. The polarized ketene approaches the *si* face of the enamide, as the *re* face is blocked by π-shielding with the aryl group as shown in Figure 38.

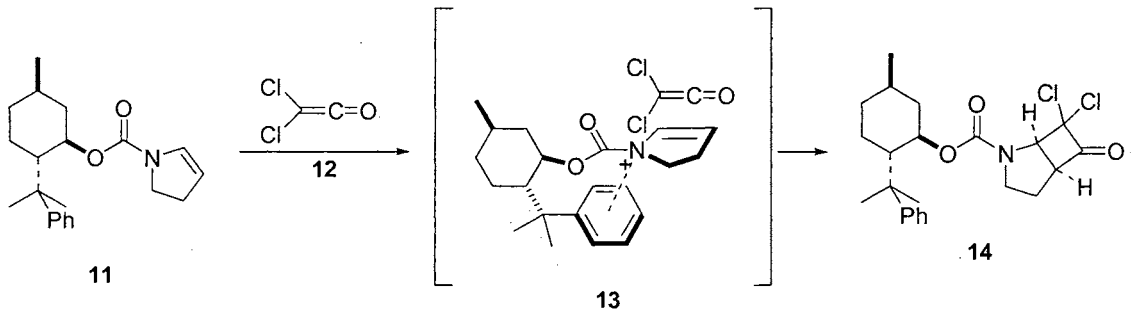


Figure 38. [2+2] Cycloaddition of dichloroketene **12**.

Conjugate Additions

Kibayashi and co-workers[64] have reported a comprehensive screen of 8-phenylmenthol analogs for the conjugate allylation of *N*-acyl-2,3-dihydro-4-pyridone derivatives **15** has been performed as shown in Figure 39.

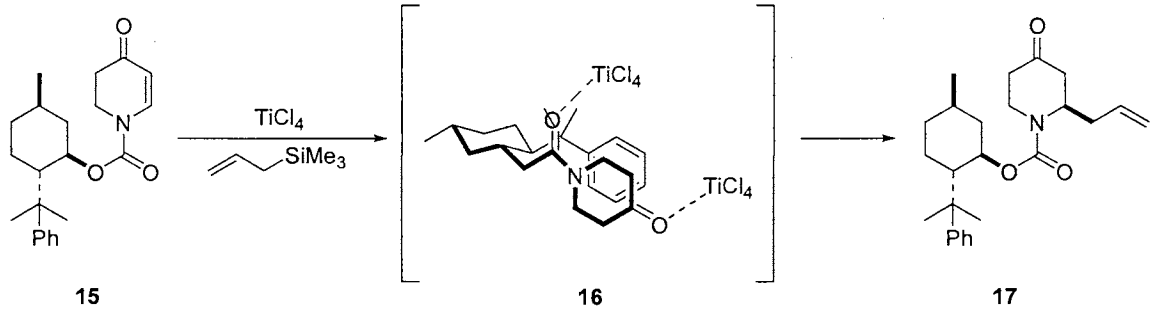


Figure 39. Conjugate allylation of *N*-acyl-2,3-dihydro-4-pyridone.

Berkowitz and co-workers[65] conducted a study of the asymmetric alkylation of vinyl glycine-derived dianions using various cyclohexyl auxiliaries. For substrate **18**, optimal selectivity was obtained with 2-naphthyl as the aryl group. The results of this study suggest a favorable rotamer population involving face-face vinyl-aryl π-π interactions of an electrostatic nature. This could involve the *exo*-extended arrangement shown in **19**, which would promote *si* face alkylation to give **20** as shown in Figure 40.

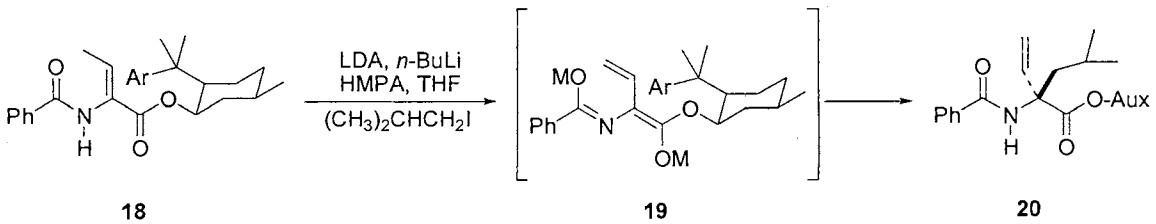


Figure 40. Asymmetric alkylation of vinylglycine derived dianions.

Carbocyclizations

A series of asymmetric radical cyclizations involving a range of chiral auxiliaries were investigated by Tsai and co-workers.[66] Under optimal conditions, the 8-phenylmenthol-derived sulfide **21** underwent 5-*exo*-trig cyclization to give **23** with high diastereoselectivity. The authors attributed the high selectivity obtained with (-)-8-phenylmenthol due to the phenyl group in the chiral auxiliary of **21** effectively shielding the *si* face of the incipient radical center in **22**, leading to a *re* face attack as shown in Figure 41.

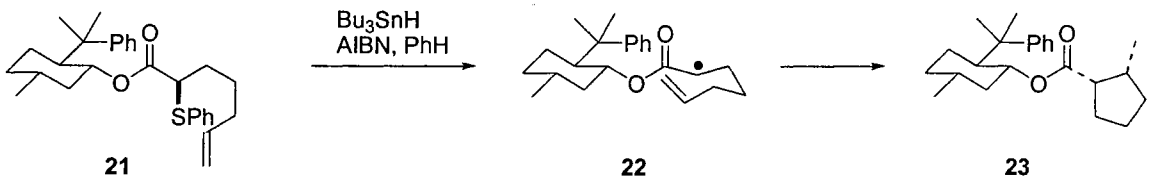


Figure 41. Radical cyclizations of 8-phenylmenthol derived sulfide.

An asymmetric Pictet-Spengler reaction has been reported by Comins and co-workers.[67] Carbamate **24** underwent condensation to form **27** in 68% yield, and reductive removal of the auxiliary led to (-)-laudanosine (**27**) in 63% ee (Figure 42).

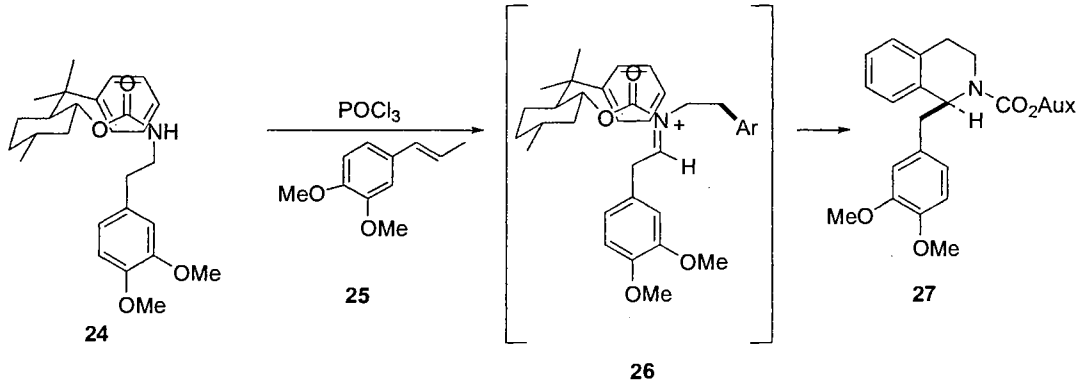


Figure 42. Asymmetric Pictet-Spengler reaction.

Other Reactions

Dai and co-workers[68] have investigated stereoselective arsenic-based Wittig-type reactions using the (-)-8-phenylmenthol auxiliary. Bromoester **28** was coupled with phenylcyclohexanone **29** to give enoate **31** in up to 80% *de* using the intermediate arsine salt. A model involving enolate **30** was proposed which shields its lower face, thereby permitting an equatorial attack on the ketone as shown in Figure 43.

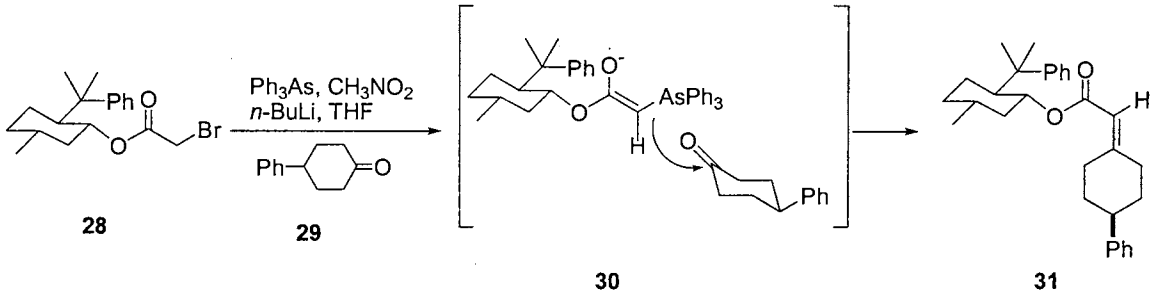


Figure 43. Stereoselective Wittig reactions.

Takagi and co-workers[69] have reported an asymmetric Darzens reaction using the α-bromoester **32** to form product **34** with a high degree of diastereoselectivity. This diasteroselectivity has been attributed to the *si* face of the *Z* enolate adding to the *si* face of the ketone as shown in **33** as shown in Figure 44.

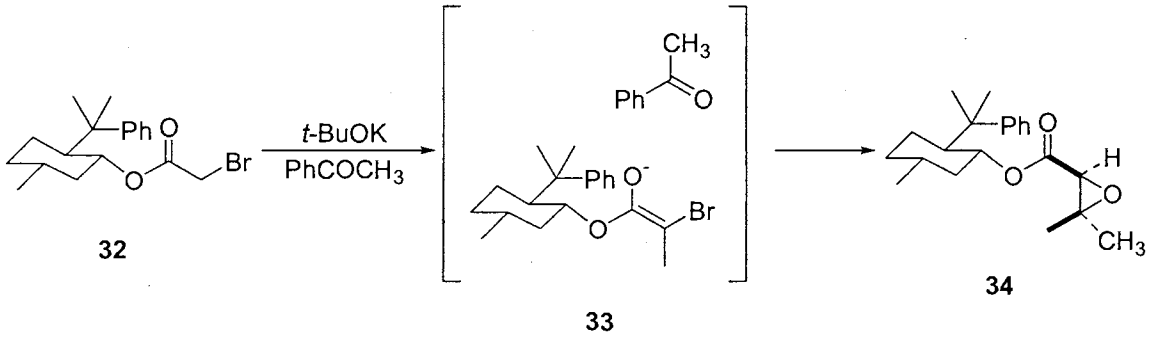


Figure 44. Asymmetric Darzen's reaction.

Esquerra and co-workers[70] have reported the Michael addition of achiral *N*-protected glycine esters to an 8-phenylmenthol-derived Fischer alkenylcarbenes. Addition of **35** and **36** proceeded with good diastereoselectivity. The authors proposed that π-shielding of one face of the Michael acceptor dictates approach of the anion as shown in Figure 45.

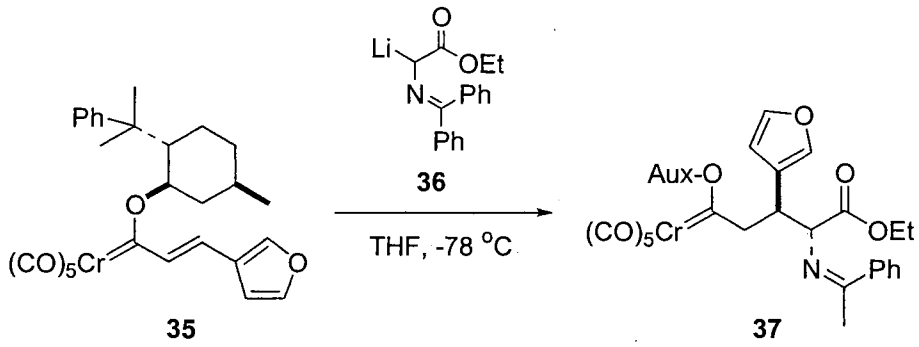


Figure 45. Michael addition of achiral *N*-protected glycine esters.

CHAPTER IV

CHIRAL 1,2,3,4-TETRAHYDROQUINOLINE-CARBOXYLATE ESTERS BY A TANDEM REDUCTION-REDUCTIVE AMINATION

Introduction

The tetrahydroquinoline nucleus is found in a wide range of biologically active compounds[70-72] and is an important building block for more complex natural products. Bunce and co-workers[73] have described a tandem reduction-Michael addition reaction for the synthesis of tetrahydroquinoline-4-carboxylate esters. This last reference notes the formation of the tetrahydroquinoline esters with a high degree of diastereoselectivity. It was hypothesized that if the synthesis involved an optically active substrate, it would result in the formation of a single isomer of an optically active tetrahydroquinoline. To synthesize an optically active heterocyclization substrate, (-)-8-phenylmenthol was employed as a chiral auxiliary for asymmetric induction.

Synthesis of (-)-8-Phenylmenthol. Commercially available technical grade (+)-(*R*)-pulegone (**1**) was subjected to a conjugate addition of phenylmagnesium bromide in the presence of freshly purified copper(I)bromide. This resulted in a conjugate 1,4-addition

to give a mixture of *cis* and *trans* 8-phenylmenthone. This mixture was then subjected to an equilibriation step to afford a 70:30 mixture of **2** and **3** respectively.

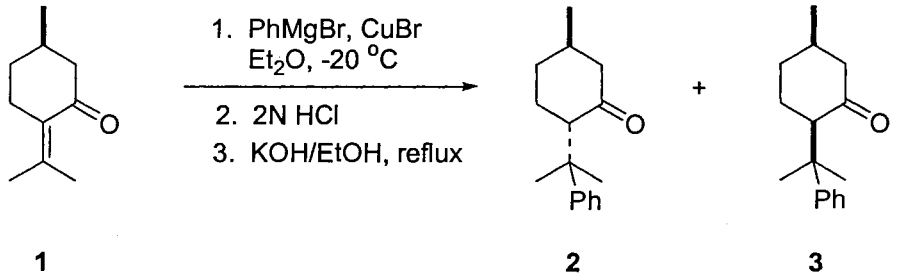


Figure 46. 1,4-Addition of phenylmagnesium bromide to (+)-(*R*)-pulegone.

The equilibrated mixture of ketones was then reduced using metallic sodium and isopropyl alcohol to yield the mixture of alcohols **4** and **5**. This mixture was esterified using DMAP in dichloromethane in presence of triethylamine at 0 °C, in a departure from the reported procedure of Ort.[74] Work-up followed by careful crystallization, gave the chloroacetate diastereomer **6** in its optically pure form.

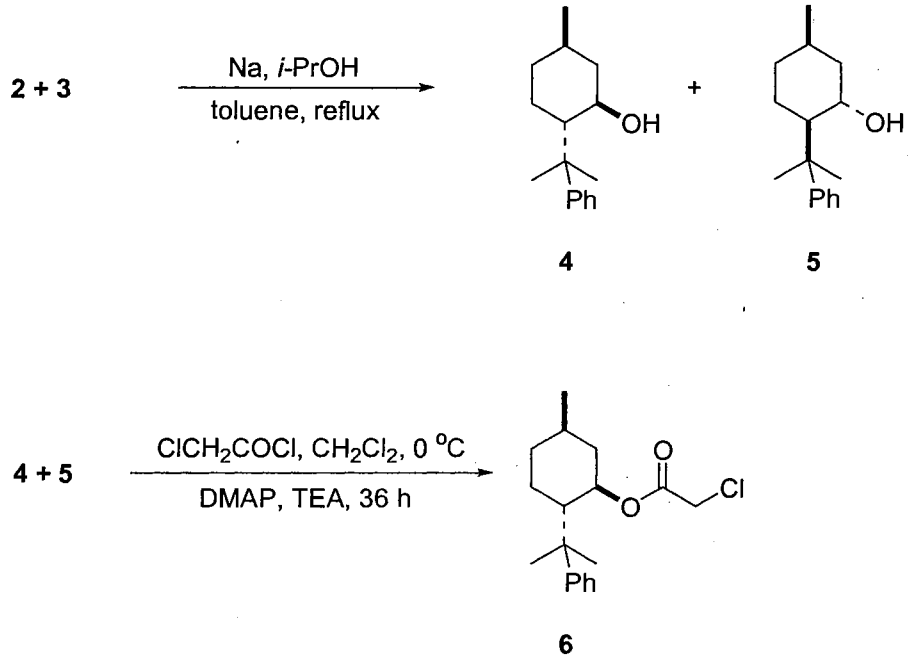


Figure 47. Synthesis of chloroacetate diastereomer of (-)-8-phenylmenthol.

Chloroacetate **6** was then subjected to basic hydrolysis, followed by vacuum distillation to afford optically pure (-)-8-phenylmenthol.

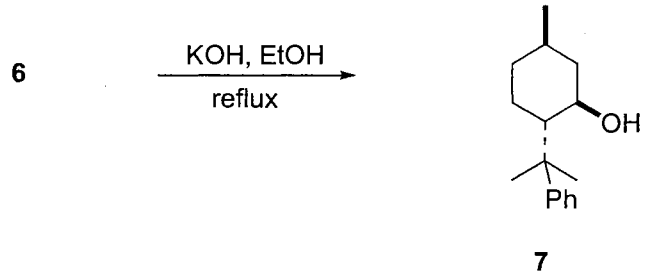


Figure 48. Synthesis of (-)-8-phenylmenthol.

Synthesis of (-)-8-phenylmenthyl ester of 2-nitrophenylacetic acid. A reaction between thionyl chloride and 2-nitrophenylacetic acid (**8**) resulted in the formation of the acid chloride. This reaction was carried out in an oil bath at 78-80 °C. After refluxing for 8 h, the excess of thionyl chloride was removed using dry benzene as the chaser liquid.

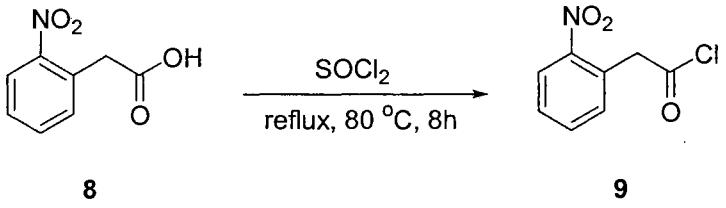
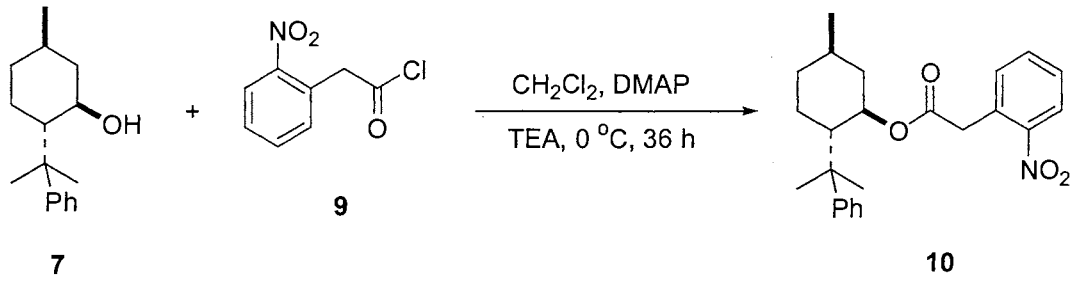


Figure 49. Synthesis of acid chloride of 2-nitrophenylacetic acid.

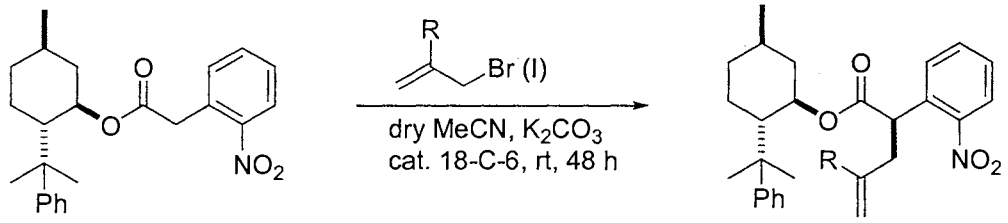
The acid chloride **9**, was then esterified with optically pure **7** in the presence of DMAP and triethylamine in dichloromethane at 0 °C. Chromatographic separation gave the ester **10** as a single enantiomer ($[\alpha]_D^{23}$ = -24.6°) as judged by ^{1}H-NMR and ^{13}C-NMR spectroscopy.



7 9 10

Figure 50. Synthesis of 2-nitrophenylacetyl ester of (-)-8-phenylmenthol.

Synthesis of the Cyclization Substrates. The cyclization substrates were prepared by alkylation of the 8-phenylmenthyl ester of 2-nitrophenylacetic acid with various substituted allylic halides as shown in Figure 51. This reaction was carried out using anhydrous potassium carbonate in dry acetonitrile at 0-5 °C containing a catalytic amount of 18-crown-6.[75] The yields ranged from 76-82%, depending on the nature of the substituent, and are summarized in Table I.



10 22-27

Figure 51. Alkylation of 2-nitrophenylacetyl ester of (-)-8-phenylmenthol with substituted allyl halides.

TABLE I

THE ALKYLATION OF 2-NITROPHENYLACETYL ESTER OF (-)-8-PHENYLMENTHOL BY 2-SUBSTITUTED ALLYL HALIDES

Starting allyl halide	R	X	Product	% Yield
11	H	Br	**22**	85
12	Me	I	**23**	80
13	*n*-Bu	Br	**24**	84
14	*t*-Bu	Br	**25**	76
15	Ph	I	**26**	79
21	2-methyl-cyclopentenyl	Br	**27**	76

Treatment of the substituted nitro esters with ozone in methanol[76] at -78 °C, followed by treatment with *p*-toluenesulfonic acid as shown in Figure 52, afforded the nitro ketones in yields of 85-89% (Table II). This acid treatment also served to remove the formaldehyde produced as a second product in the ozonolysis.

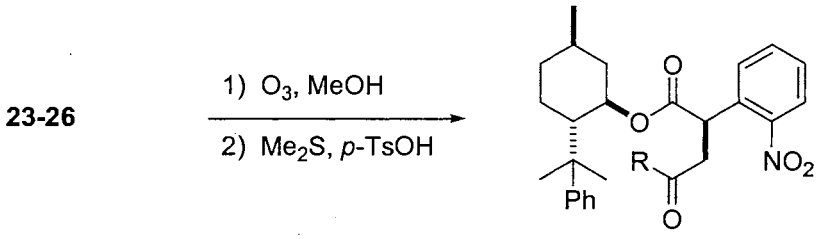


Figure 52. Ozonolysis of allyl substituted 2-nitrophenylacetyl esters.

In the case of the simple allyl substituted substrate, ozonolysis in methanol, followed by treatment with *p*-toluenesulfonic acid, generated the aldehyde dimethyl acetal.

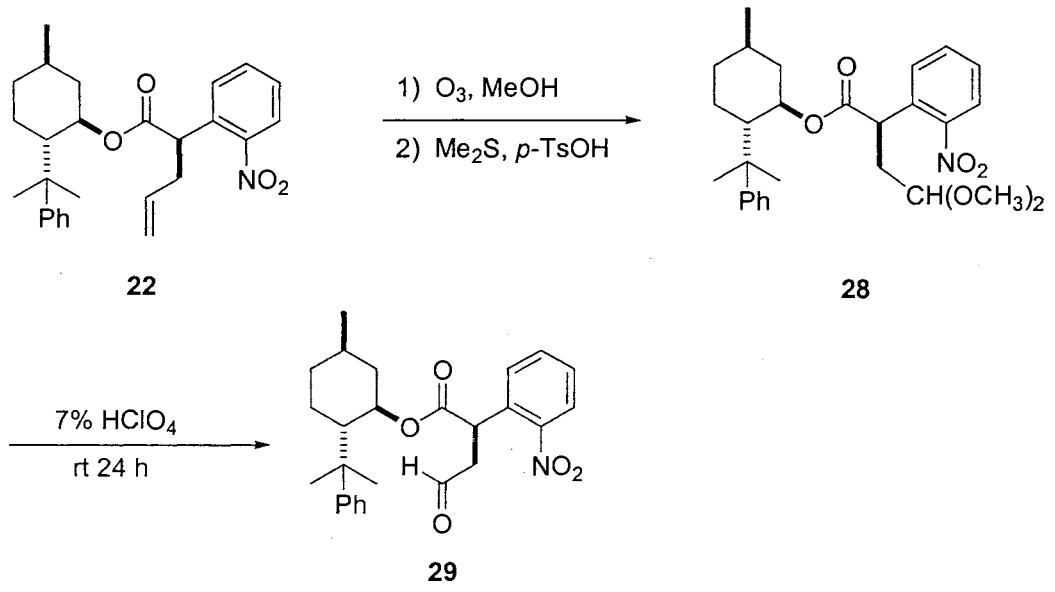
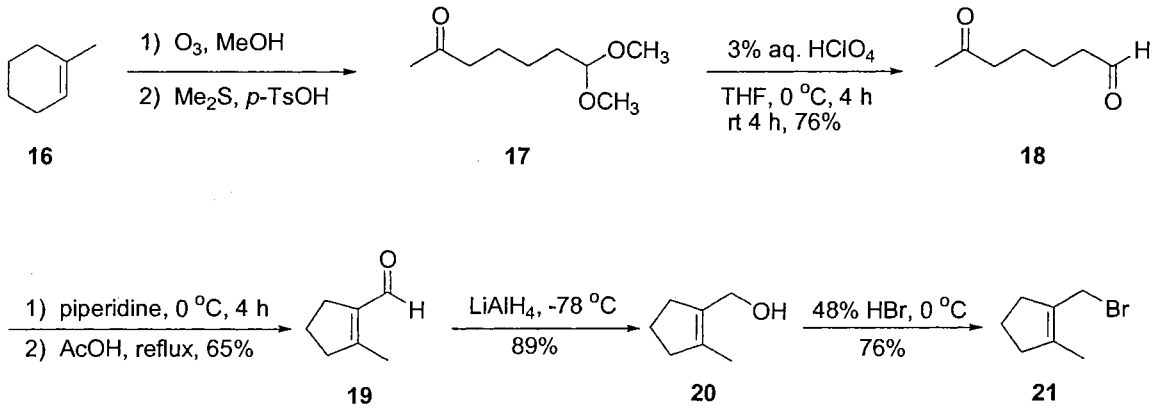


Figure 53. Ozonolysis of simple allyl substituted 2-nitrophenylacetyl ester.

Compound **28** was more easily isolated from the ozonolysate than the aldehyde.[77] Prior to reductive cyclization, the acetal was treated with 7% aqueous $HClO_4$ in THF (1:1 v/v)[77] for conversion to the aldehyde **29** as shown in Figure 53.

The synthesis of 1-bromomethyl-2-methylcyclopentene (**21**) was carried out starting from 1-methylcyclohexene (**16**), which was subjected to an ozonolysis[77,78] procedure to yield the ketoacetal **17**. The ketoacetal was converted to the ketoaldehyde **18** which was reacted with piperidine, followed by acetic acid reflux, to afford cyclopentene-1-carboxaldehyde (**19**). This aldehyde was then subjected to a reduction to yield the alcohol **20**. Alcohol **20** was treated with 48% aq. HBr at 0 °C to yield the required alkylating agent **21** as shown in Figure 54.



16 17 18 19 20 21

Figure 54. Synthesis of 1-bromomethyl-2-methylcyclopentene.

The chiral nitro ester **10** was alkylated with **21** using the same procedure as previously reported to give the alkylated nitro ester **27**. The alkylated nitro ester **27** was then subjected to an ozonolysis to afford the diketone **34** as shown in Figure 55.

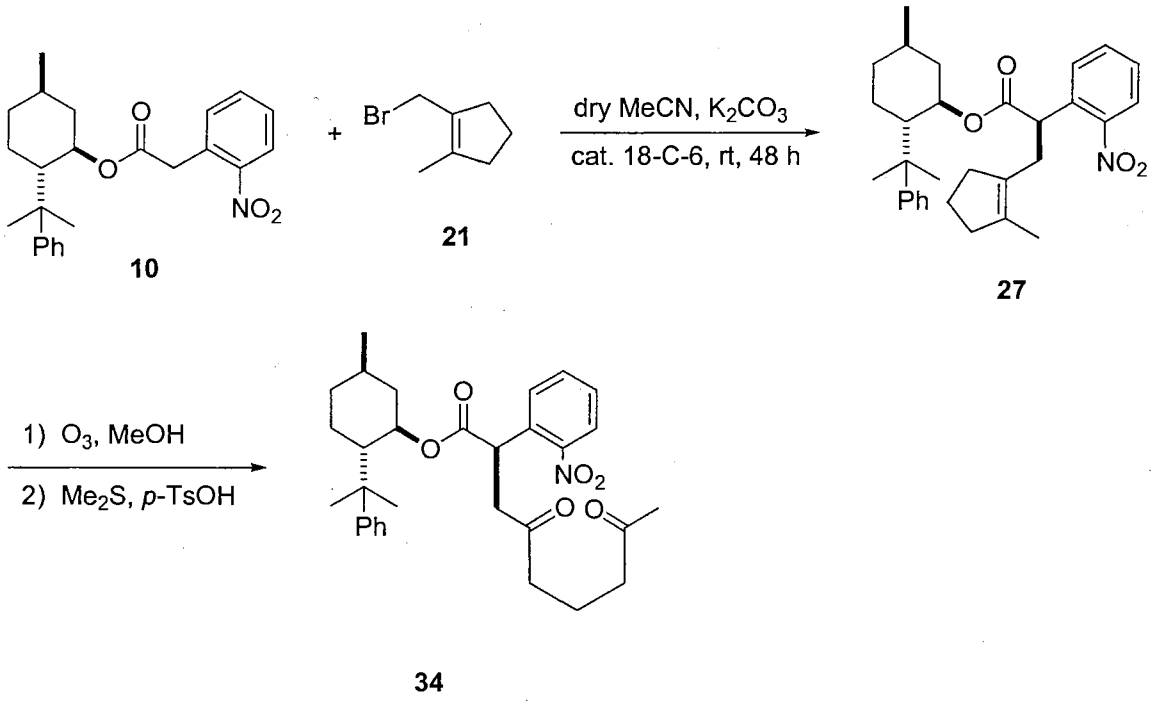


Figure 55. Alkylation of 2-nitrophenylacetyl ester of (-)-8-phenylmenthol ester by 1-bromomethyl-2-methylcyclopentene followed by ozonolysis.

TABLE II

OZONOLYSIS OF ALLYL SUBSTITUTED 2-NITROPHENYLACETYL ESTER OF (-)-8-PHENYLMENTHOL

Starting alkene	R	Product	% Yield
22	H	**29**	86
23	Me	**30**	85
24	*n*-Bu	**31**	88
25	*t*-Bu	**32**	87
26	Ph	**33**	89
27	2-methylcyclopentenyl	**34**	86

Results

Reductive cyclization of the nitro ketones under catalytic hydrogenation conditions[79,80] (Figure 56) afforded the chiral 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylates **36-39** in yields ranging from 79-82% as shown in Table III.

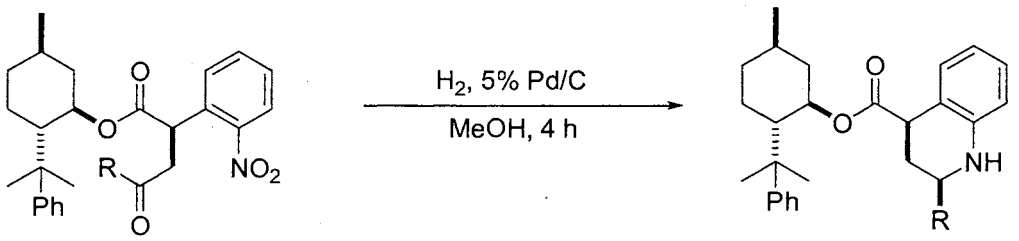


Figure 56. Tandem reduction-reductive amination of nitro ketones.

Catalytic hydrogenation of the aldehyde substrate (Figure 57) gave (-)-8-phenylmenthyl 1,2,3,4-tetrahydroquinoline-4-carboxylate (**35**) in 84% yield.

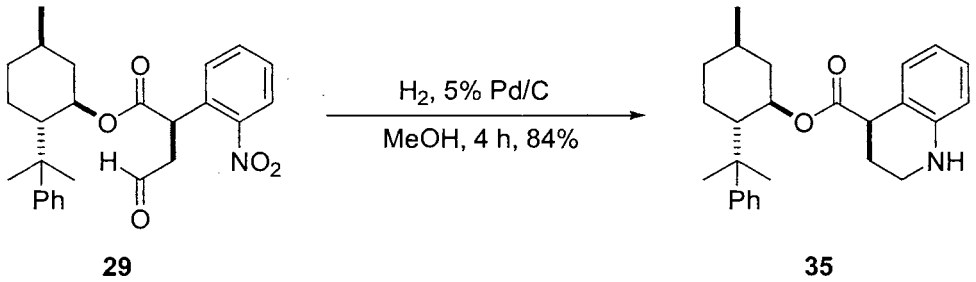
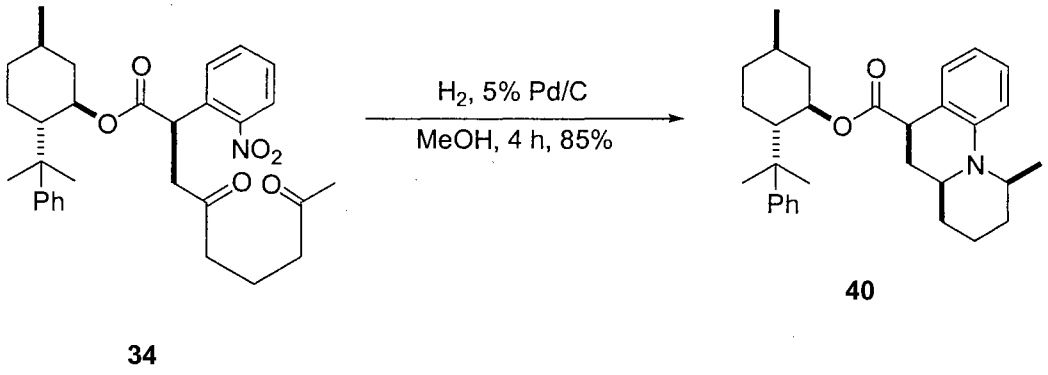


Figure 57. Tandem reduction-reductive amination of aldehyde substrate.

This procedure was further extended to the synthesis of the 1-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate ester (**40**) from diketone **34**. Hydrogenation of the diketone afforded the angular-fused tricyclic product **40** in 85% yield as shown in Figure 58.



34 40

Figure 58. Tandem reduction-reductive amination to form tricyclic compound.

Table III

TANDEM REDUCTION-REDUCTIVE AMINATION OF NITROKETONES

Starting ketone	R	Product	% Yield
29	H	**35**	84
30	Me	**36**	82
31	*n*-Bu	**37**	81
32	*t*-Bu	**38**	79
33	Ph	**39**	79
34	4-oxopentyl	**40**	85

To demonstrate the utility of this method and to prove that the chiral auxiliary could be recycled, it was necessary to cleave the ester and to assay the chirality of the products. Reduction of the ester group in **40** with lithium aluminum hydride in THF resulted in the formation of the chiral tricyclic alcohol in 81% yield as shown in Figure 59. Chromatography resulted in 82% recovery of the (-)-8-phenylmenthol. The recovered (-)-8-phenylmenthol had the same optical rotation ($[\alpha]_D^{23} = -26.4^o$) as that of the starting chiral auxiliary. Hence (-)-8-phenylmenthol can be recycled.

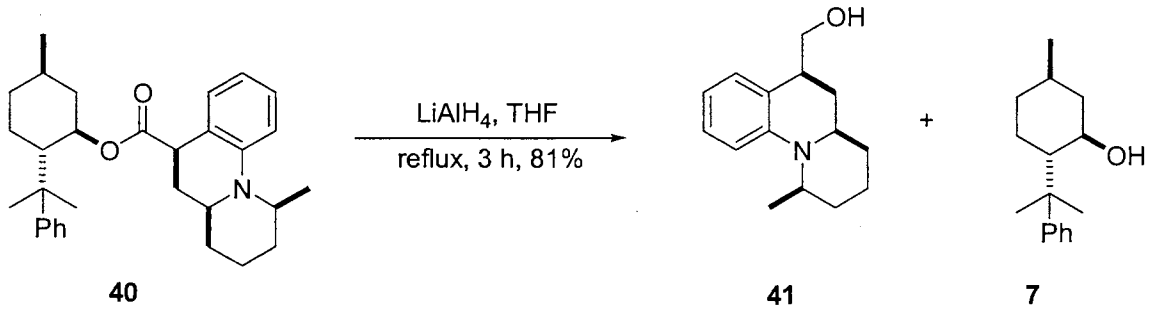


Figure 59. Cleavage of (-)-8-phenylmenthyl ester group to form quinolizine.

Mechanism of Ring Closure In presence of 5% palladium-on-carbon, the aromatic nitro group was reduced by hydrogen to the hydroxylamine. This amino group forms an imine **43** with the carbon of the carbonyl group (Figure 60).

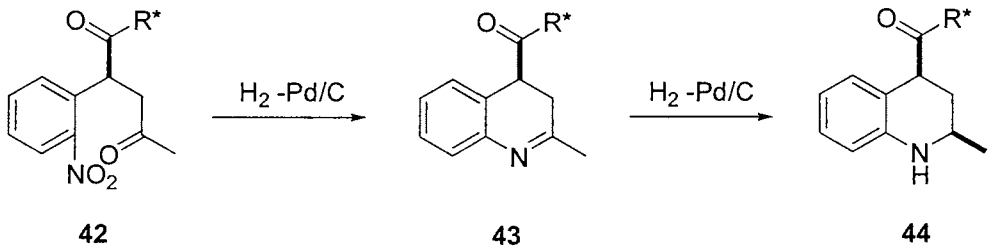


Figure 60. Mechanism of tandem reduction-reductive amination.

Once the imine is formed, another molecule of hydrogen adds to the imine double bond from the plane below the carbon-nitrogen double as shown in Figure 60. The steric bulk of the ester in the 4-position forces the hydrogen to add to the double bond in this manner.[79,80] Consequently, the substituent in the 2-postion is pushed above the plane making it cis to the ester group at the C-4 position.

Discussion. The key step in the synthesis is the asymmetric allylation of (-)-8-phenylmenthyl 2-nitrophenylacetate. The choice of (-)-8-phenylmenthol as a chiral auxiliary was guided by the hypothesis that the pendant phenyl ring of (-)-8-phenylmenthol should act to shield one face of the molecule and hence function as a stereodirector during the alkylation reaction. When the alkylation was carried out at 0-5 ^{o}C in dry acetonitrile in the presence of excess anhydrous potassium carbonate, the selectivity was high for the formation of a single product isomer. The stereochemical purity was most easily assessed by using ^{1}H and ^{13}C NMR spectroscopy. At reflux temperatures, selectivity was dramatically reduced. The formation of a mixture of enantiomers could be attributed to the loss of the π-stacking effect[81] of the phenyl ring of (-)-8-phenylmenthol. The size of the alkylating agent also had an effect on the yield of the alkylated ester. Larger alkylating agents tended to give lower yields, possibly due to steric interaction with the bulky (-)-8-phenylmenthyl group. The ring closure reactions proceeded in good yields and were highly selective. Presumably, the presence of the bulky (-)-8-phenylmenthyl ester group causes a steric effect resulting in the delivery of hydrogen trans to the ester group. This leads to the formation of a product having the C-2 alkyl group and the C-4 ester group cis to one another. The asymmetric alkylation takes place using anhydrous K_2CO_3 in dry acetonitrile containing 18-crown-6 at 0-5 ^{o}C,

conditions that favor the formation of a "naked" enolate. The importance of the "naked" enolates in asymmetric alkylations has been previously recognized,[82] and the selectivity has been attributed to their tendency to remain free of aggregated species. The earlier report described the alkylation of phenyl acetate esters at -100 °C using *t*-Bu-P4 base.[83] Conditions employed in the work described in this part of the thesis allow for the use of much higher temperatures, but the reaction is still sensitive to temperature. As previously reported, no dialklylation was observed.[84] In the last case, removal of the chiral auxiliary gave the chiral tricyclic alcohol **41** in 81% yield using lithium aluminum hydride. The alcohol was separated from (-)-8-phenylmenthol by flash chromatography. Both ^{1}H and ^{13}C NMR analysis of the tricyclic alcohol showed only one enantiomer of the product. GC analysis also showed a single peak. The chiral auxiliary was obtained in a yield of 82% and the optical rotation was identical to that of the starting material.

Conclusion. This work provides a new synthetic approach to chiral 1,2,3,4-tetrahydroquinoline-4-carboxylate esters and 1-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate ester. The key step in the synthesis is the asymmetric allylation of the "naked" anion of (-)-8-phenylmenthyl 2-nitrophenylacetate at 0 °C. Following ozonolysis of the double bond, the synthesis culminates in a tandem reaction sequence triggered by the reduction of the aromatic nitro group which then undergoes reductive amination with the carbonyl group(s). The recovery of (-)-8-phenylmenthol with the same optical activity after reduction allows for recycling of the chiral auxiliary. This methodology can be furthered to explore asymmetric induction in other substitution patterns to construct more complex ring systems.

Acknowledgments. Support of this work by the Oklahoma Center for the Advancement of Science and Technology (HR01-015) is greatly appreciated. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometer by the NIH and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

EXPERIMENTAL SECTION

Commercial reagents and solvents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The HCl (2 *M*), $NaHCO_3$ (saturated), NaCl (saturated) and Na_2SO_4 (saturated) used in various procedures refer to aqueous solutions. Reactions were monitored by TLC on silica gel GF plates (Analtech no. 21521) or capillary GC (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) with FI detection programmed between 50-300 °C. Preparative separations were performed using flash column chromatography on silica gel (grade 62, 60-200 mesh) mixed with UV-active phosphor (Sorbent Technologies no. 5) or PTLC on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015); band elution was monitored by using a hand-held UV lamp. All IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. Both ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$; coupling constants (*J*) have been given in Hz. Optical rotations were measured on Perkin-Elmer 241 Polarimeter, in the solvents delineated and in concentrations of g/100 mL. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 ev.

(2*RS*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone (2, 3). In a nitrogen flushed, 1000-mL, three-necked, round-bottomed reaction flask fitted with an overhead stirrer, reflux condenser and a $CaCl_2$ guard tube and a 250 mL pressure equalizing dropping funnel was placed 5.50 g (0.23 mol) of magnesium turnings and 50 mL of ether. To this flask 4.00 g (25.5 mmol) of bromobenzene was added in one portion and the reaction was warmed to start the formation of the Grignard reagent. Once the reaction had started, 35.3 g (0.22 mmol) of bromobenzene in 100 mL of ether was added dropwise

at a rate which maintained a gentle reflux. After the addition was complete, the reaction was refluxed for one hour. The solution was allowed to cool to room temperature, and 300 mL of ether were added. The reflux condenser and the dropping funnel were then replaced by a nitrogen inlet tube and a pierced rubber septum with a stainless tube inlet.

In a second nitrogen flushed, 1000-mL, three-necked, round-bottomed flask, fitted with an overhead stirrer, a reflux condenser and with a $CaCl_2$ guard tube, and a rubber septum with a stainless tube inlet connected to the first flask was placed 2.20 g (15.5 mmol) of copper(I) bromide and 100 mL of ether. The system was cooled to -5 °C. To this vigorously stirred suspension of copper(I) bromide and 50 mL of diethyl ether, the ethereal Grignard reagent from the first flask was added by a positive nitrogen diplacement. Once the addition was complete, the reaction mixture was stirred at -5 °C for 30 min. The rubber septum was then replaced by a pressure equalizing dropping funnel containing 20.0 g (0.13 mol) of (*R*)-(+)-pulegone (**1**) in 50 mL of ether. This solution was added with stirring at -5 °C to the dark green reaction mixture over 2 h. After the addition was complete the reaction mixture was kept stirring overnight at -5 °C, and was added to an ice-cold solution of 2 *M* HCl with vigorous stirring. The organic layer was separated, and filtered with suction and the residue on the funnel was washed with 25 mL portions of ether (3x). The aqueous layer was saturated with 20 g of solid NH_4Cl and washed with 100 mL of ether (3x). The combined organic layers were collected and washed with 20 mL of $NaHCO_3$, 25 mL of NaCl and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give 29.70 g (0.128 mol, 98%) of an oil which was used directly for equilibriation without purification.

A solution of 29.7 g (128 mmol) of the crude oil obtained in the previous step was dissolved in 300 mL of anhydrous EtOH, containing 40 mL of H_2O and 35.0 g (623 mmol) of KOH pellets, and he solution was refluxed for 8 h. The reaction mixture was then allowed to cool to room temperature and concentrated to a volume of 100 mL, and 200 mL of H_2O was added to it. This aqueous solution was saturated with 25 g of solid NaCl and extracted with 50 mL portions of ether (5x). The organic layers were combined, then dried ($MgSO_4$), concentrated, and vacuum distilled. Vacuum distillation yielded three fractions: the first fraction (boiling range 40-80 °C, 0.05 mm) was discarded. The second fraction (boiling range 80-100 °C, 0.05 mm) consisted mainly of biphenyl. The third fraction (boiling range 105-110 °C, 0.05 mm) yielded 27.5 g (119 mmol, 93%) of equilibrated ketones **2** and **3**.

(1*RS*,2*SR*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (4, 5). In a 1000- mL, three-necked, round-bottomed flask fitted with an over-head stirrer, a reflux condenser fitted with a $CaCl_2$ guard tube, and a 250 mL pressure equalizing dropping funnel was placed 8.00 g (350 mmol) of Na and 110 mL of toluene. The reaction mixture was heated to reflux in an oil-bath (temperature of 120-125 °C), and a vigorous stirring resulted in a fine dispersion of Na. To this vigorously stirred dispersion, was added at a controlled rate, a solution of 27.5 g (119 mmol) of equilibrated ketones **2** and **3** in 20.4 g (28.0 mL, 340 mmol) of 2-propanol. The solution was heated at a gentle reflux. After the addition was complete, the reaction mixture was refluxed for a further period of 8 h, allowed to cool to room temperature and further cooled to 0 °C. The reaction mixture was then diluted with 100 mL of ether, and the reaction mixture was carefully poured into 300 mL of ice cold H_2O. The organic layer was separated, and the aqueous layer was

saturated with 15 g of solid NaCl and extracted with 100 mL portions of ether (4x). The organic layers were combined, washed with 25 mL of NaCl, then dried ($MgSO_4$), filtered and concentrated. Vacuum distillation of the oil gave 26.9 g (116 mmol, 97 %) of a pale yellow oil (boiling range 102-107 °C, 0.1mm) consisting of **4** and **5**.

(1*RS*,2*SR*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexylacetate (6). In a 500-mL, three-necked, round-bottomed flask, fitted with a reflux condenser with a guard tube, a 100 mL pressure equalizing dropping funnel and a Teflon coated magnetic stir bar was placed 26.9 g (116 mmol) of the mixture of **4** and **5** in 50 mL of CH_2Cl_2, 1.41 g (11.5 mmol) of DMAP and 17.6 g (24.2 mL, 174 mmol) of triethylamine. The solution was cooled in an ice bath to 0 °C. To this cold stirred solution was added dropwise a solution of 19.7 g (13.9 mL, 174 mmol) of chloroacetyl chloride in 15 mL of CH_2Cl_2 over a period of 2 h at a rate such that the temperature remained below 0 °C. After the addition was complete, the reaction was maintained at 0 °C for 2 h and then was gradually allowed to warm to room temperature with stirring for 36 h. The reaction mixture was concentrated under reduced pressure to yield a reddish brown solid to which 100 mL of ether was added. The insoluble solids which separated were filtered. The ethereal filtrate was washed with 20 mL of 2 *M* HCl (2x), 15 mL of $NaHCO_3$, 20 mL of NaCl, then dried ($MgSO_4$) and concentrated under reduced pressure to yield 34.2 g (104 mmol, 90%) of a pale yellow oil **6** which crystallized upon addition of 90% ethanol. The mixture was refrigerated for 24 h to maximize the yield and then was filtered to afford 17.9 g (58.0 mmol, 50%) of the chloroacetate **6** as a pure diastereomer. Mp 83-84 °C, $[\alpha]^{23}_D$ +22.5°·(*c* = 2.28, CCl_4); IR 1760 cm^{-1}; ^1H NMR δ 7.33-7.11 (m, 5 H), 4.90 (dt, 1 H, *J* = 10.8, 4.6 Hz), 3.34 (ABd, 1 H, *J* = 14.9 Hz), 3.00 (ABd, 1 H, *J* = 14.9 Hz), 2.12-2.03 (m, 1 H),

1.92-1.79 (m, 2 H), 1.73-1.61 (complex, 1 H), 1.50-1.43 (br s, 1 H), 1.31 (s, 3 H), 1.19 (s, 3 H), 0.88 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 166.5, 151.7, 128.0, 125.2, 125.1, 75.77, 50.2, 41.4, 40.8, 39.4, 34.3, 31.2, 29.7, 26.1, 22.6, 21.7.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (7). In a 1000-mL, round-bottomed flask fitted with a reflux condenser and a Teflon coated magnetic stir bar was placed 17.9 g (58.0 mmol) of **6** was dissolved in 400 mL of EtOH containing 80 mL of H_2O, and 9.20 g (164 mmol) of KOH pellets. This solution was refluxed for 8 h and concentrated to a volume of 50 mL, and 100 mL of ether and 200 mL of H_2O were added. The ether layer was separated, and the aqueous phase was saturated with 25 g of solid NaCl and extracted with 50 mL of ether (4x). The ether layers were combined, washed with 25 mL of NaCl, then dried ($MgSO_4$), and concentrated to give a yellow oil. Vacuum distillation (boiling range 105-108 °C at 0.05 mm) yielded 13.2 g (56.8 mmol, 98%) of pure (-)-8-phenylmenthol (**7**) with following physical properties. $[\alpha]_D^{23}$ -26.4° (c = 2.00, C_2H_5OH). IR 3570, 3417 cm^{-1}; ^{1}H NMR δ 7.46-6.97 (m, 5 H), 3.48 (dt, 1 H, J = 10.24, 4.26 Hz), 1.87-1.79 (br s, 1 H), 1.75-1.56 (complex, 4 H), 1.42 (s, 3 H), 1.29 (s, 3 H) 0.87 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 151.24, 128.39, 125.74, 125.71, 72.92, 54.07, 45.25, 39.71, 34.81, 31.44, 28.64, 26.42, 24.20, 21.96.

2-Nitrophenylacetyl chloride (9). Although no problems were experienced, this compound is reported to be explosive in its pure form at temperatures above 80 °C.[85] In an oven-dried, 250-mL, round-bottomed flask fitted with a reflux condenser with a calcium chloride guard tube and a Teflon coated magnetic stir bar was placed 2.00g (11.0 mmol) of 2-nitrophenylacetic acid (**8**) and 15 mL of $SOCl_2$. The mixture was refluxed for 8 h, while ensuring that the temperature of the oil bath did not exceed 80 °C. Excess

$SOCl_2$ was removed by distillation under reduced pressure using benzene as a chaser liquid to yield 2.10 g (10.6 mmol, 96%) of **9** as a red oil which was used immediately for the next step without further purification.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl 2-Nitrophenylacetate (10). To a stirred solution of 1.50 g (6.47 mmol) of (-)-8-phenylmenthol (**7**), 0.09 g (0.74 mmol) of DMAP and 1.07 g (1.47 mL, 10.59 mmol) of TEA in 25 mL of CH_2Cl_2 at 0 °C was added dropwise an ice-cold solution of 2.10 g (10.59 mmol) of **9** in 10 mL of CH_2Cl_2. The reaction was maintained at 0 °C for 2 h and then was allowed to warm to room temperature with stirring for 30 h. The reaction mixture was concentrated, and an orange red residue was obtained. This residue was dissolved in 50 mL of ether and washed with 20 mL portions of H_2O (2x). The ether layers were collected and washed with 10 mL of 2 *M* HCl, 15 mL of $NaHCO_3$, then dried ($MgSO_4$). Concentration gave a viscous oil that was chromatographed on a 50 cm x 2 cm silica gel column eluted with hexane:ether (98:2) to afford 2.25 g (5.69 mmol, 88%) of **10**. $[\alpha]_D^{23}$ -24.6° (*c* = 0.55, $CHCl_3$). IR 1732, 1530, 1349 cm^{-1}; ^1H NMR δ 8.02 (dd, 1 H, *J* = 8.1, 1.1 Hz), 7.51 (td, 1 H, *J* = 7.6, 1.4 Hz), 7.38 (td, 1 H, *J* = 7.9, 1.4 Hz), 7.31 (m, 5 H), 7.16 (m, 1 H), 4.83 (td, 1 H, *J* = 10.7, 4.4 Hz), 3.51 (ABd, 1 H, *J* = 17.3 Hz), 3.19 (ABd, 1 H, *J* = 17.3 Hz), 2.05 (td, 1 H, *J* = 11.0, 3.4 Hz), 1.90 (br d, 1 H, *J* = 12.1 Hz), 1.72 (dd, 1 H, *J* = 13.2, 3.4 Hz), 1.62 (br d, 1 H, *J* = 12.8 Hz), 1.42 (m, 2 H), 1.28 (s, 3 H), 1.18 (s, 3 H), 0.86 (m, 2 H), 0.86 (m, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 169.0, 151.6, 148.8, 133.1 (2), 129.8, 128.2, 127.8, 125.6, 125.4, 124.9, 75.0, 50.0, 41.3, 39.5, 39.2, 34.3, 31.1, 28.4, 26.3, 24.1, 21.7; HRMS *m/z* calcd for $C_{24}H_{29}NO_4$: 395.2096, found: 395.2095.

Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.91; H, 7.34. Found: C, 72.68; H, 7.45.

Representative Procedure for Alkylation of (1*R*, 2*S*, 5*R*)-8-Phenylmenthyl 2-Nitrophenylacetate: (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-2-(2-Nitrophenyl)-4-pentenoate (22). The general procedure of Makosza and Tyrala was used.[75] To a stirred solution of 1.50 g (3.80 mmol) of **10** in 20 mL of dry MeCN maintained at 0-5 °C was added 5.92 g (42.8 mmol) of anhydrous K_2CO_3 and 15 mg of 18-crown-6. To the resulting blue mixture was added a solution of 0.59 g (4.87 mmol) of allyl bromide (**11**) in 5 mL of dry MeCN. The reaction was stirred at 0-5 °C for 8 h, and the solids were filtered. The filtrate was concentrated to yield an oil. The crude oil was determined to be a single isomer by ^{1}H and ^{13}C NMR spectroscopy. Final purification of the crude oil was carried out on six 20 cm x 20 cm PTLC plates eluted with hexane:ether (95:5), to give 1.40 g (3.22 mmol, 85%) of **22** as a yellow oil, $[\alpha]_D^{23}$ = -23.6° (*c* = 0.55, $CHCl_3$); IR 1722, 1530, 1353 cm^{-1}; ^{1}H NMR δ 7.86 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.51 (td, 1 H, *J* = 8.0, 1.4 Hz), 7.46 (dd, 1 H, *J* = 7.8, 1.5 Hz), 7.36 (td, 1 H, *J* = 7.8, 1.4 Hz), 7.20 (m, 4 H), 7.12 (m, 1 H), 5.58 (ddt, 1 H, *J* = 17.0, 9.8, 7.1 Hz), 4.93 (dt, 1 H, *J* = 15.8, 1.4 Hz), 4.81 (dt, 1 H, *J* = 10.7, 4.4 Hz), 3.85 (t, 1 H, *J* = 7.3 Hz), 2.50 (dm, 2 H, *J* = 19.6 Hz), 1.96 (m, 2 H), 1.55 (m, 2 H), 1.50-1.20 (complex, 3 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 0.86 (m, 2 H), 0.86 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 171.2, 151.1, 149.7, 134.6, 132.7, 132.6, 130.7, 127.9, 127.8, 125.4, 125.2, 124.6, 117.4, 76.0, 50.2, 46.3, 41.6, 39.7, 36.6, 34.4, 31.3, 26.8, 26.4, 26.1, 21.7; HRMS *m/z* calcd for $C_{27}H_{33}NO_4$: 435.2409; found: 435.2411.

Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.48; H, 7.59. Found: C, 74.33; H, 7.68.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-4-Methyl-2-(2-nitrophenyl)-4-pentenoate (23). 1.39 g (3.10 mmol, 82%); $[\alpha]_D^{23}$ = -55.3° (c = 0.85, $CHCl_3$); IR 1733, 1533, 1354 cm^{-1}; ^{1}H NMR δ 7.85 (d, 1 H, *J* = 7.8 Hz), 7.55 (m, 2 H), 7.38 (m, 1 H), 7.32-7.08 (complex, 5 H),

4.80 (td, 1 H, J = 10.7, 4.3 Hz), 4.69 (s, 1 H), 4.58 (s, 1 H), 4.13 (t, 1 H, J = 7.7 Hz), 2.64 (dd, 1 H, J = 14.3, 7.6 Hz), 2.46 (dd, 1 H, J = 14.3, 7.6 Hz), 1.91 (m, 2 H), 1.66 (s, 3 H), 1.63-1.30 (complex, 4 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.86 (m, 2 H), 0.85 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 171.5, 150.8, 149.6, 141.9, 132.8, 130.2, 127.9, 127.8, 125.4, 125.3, 125.2, 124.7, 113.0, 76.2, 50.1, 44.6, 41.5, 40.5, 39.7, 34.3, 31.2, 27.0, 26.8, 25.6, 22.2, 21.7; HRMS *m/z* calcd for $C_{28}H_{35}NO_4$: 449.2566; found: 449.2561.

Anal. Calcd for $C_{28}H_{35}NO_4$: C, 74.83; H, 7.80. Found: C, 74.59; H, 7.74.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-4-Butyl-2-(2-nitrophenyl)-4-pentenoate (24). 1.40 g (2.85 mmol, 82%); $[\alpha]_D^{23}$ = -81.5° (*c* =1.35, $CHCl_3$); IR 1733, 1533, 1355 cm^{-1}; ^{1}H NMR δ 7.84 (dd, 1 H, J = 8.1, 1.2 Hz), 7.55 (m, 2 H), 7.37 (td, 1 H, J = 8.1, 2.1 Hz), 7.21-7.06 (complex, 5 H), 4.79 (td, 1 H, J = 10.6, 4.3 Hz), 4.71 (s, 1 H), 4.62 (s, 1 H), 4.17 (t, 1 H, J = 7.7 Hz), 2.67 (dd, 1 H, J = 14.5, 7.9 Hz), 2.48 (dd, 1 H, J = 14.5, 7.3 Hz), 1.91 (m, 4 H), 1.53 (dt, 1 H, J = 12.4, 3.4 Hz), 1.43-1.25 (complex, 7 H), 1.06 (s, 3 H), 0.98 (s, 3 H), 0.90 (d, 3 H, J = 7.1 Hz), 0.87 (m, 2 H), 0.85 (d, 3 H, J = 6.4 Hz); ^{13}C NMR δ 171.6, 150.6, 149.7, 146.0, 132.9, 132.6, 130.2, 127.9, 127.8, 125.5, 125.2, 124.6, 111.6, 76.1, 50.2, 44.7, 41.6, 39.9, 39.2, 35.4, 34.4, 31.3, 29.7, 27.6, 27.0, 25.1, 22.3, 21.7, 14.0; HRMS *m/z* calcd for $C_{31}H_{41}NO_4$: 491.3035, found: 491.3029.

Anal. Calcd for $C_{31}H_{41}NO_4$: C, 75.76; H, 8.35. Found: C, 75.51; H, 8.46.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-4-*tert*-Butyl-2-(2-nitrophenyl)-4-pentenoate (25). 1.18 g (2.40 mmol, 76%); $[\alpha]_D^{23}$ = -128.0° (*c* =0.75, $CHCl_3$); mp 104-106 °C; IR 1728, 1531, 1355 cm^{-1}; ^{1}H NMR δ 7.84 (dd, 1 H, J = 8.1, 1.5 Hz), 7.58 (m, 2 H), 7.37 (td, 1 H, J = 8.1, 1.6 Hz), 7.20-7.06 (complex, 5 H), 4.88 (s, 1 H), 4.78 (td, 1 H, J = 10.6, 4.4 Hz), 4.57 (s, 1 H), 4.37 (t, 1 H, J = 7.4 Hz), 2.78 (dd, 1 H, J = 16.3, 8.1 Hz), 2.52 (dd, 1

H, J = 16.3, 6.6 Hz), 1.95-1.81 (complex, 2 H), 1.60-1.28 (complex, 4 H), 1.04 (s, 12 H), 0.92 (s, 3 H), 0.87 (m, 2 H), 0.85 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 171.9, 153.8, 150.5, 150.0, 133.2, 132.6, 129.8, 127.9, 127.8, 125.8, 125.2, 124.6, 107.6, 76.2, 50.3, 44.7, 41.5, 40.0, 36.2, 34.4 (2), 31.3, 29.0 (3), 28.3, 27.1, 24.4, 21.7; HRMS *m/z* calcd for $C_{31}H_{41}NO_4$: 491.3035, found: 491.3032.

Anal. Calcd for $C_{31}H_{41}NO_4$: C, 75.76; H, 8.35. Found: C, 75.57; H, 8.41.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-4-Phenyl-2-(2-nitrophenyl)-4-pentenoate (26). 1.51 g (2.95 mmol, 79%); $[\alpha]_D^{23}$ = -22.9° (*c* =0.70, $CHCl_3$); IR 1732, 1530, 1354 cm^{-1}; ^{1}H NMR δ 7.82 (dd, 1 H, J = 7.9, 1.1 Hz), 7.48 (td, 1 H, J = 7.6, 1.4 Hz), 7.37-7.06 (complex, 12 H), 5.17 (s, 1 H), 4.96 (s, 1 H), 4.81 (td, 1 H, J = 10.6, 4.4 Hz), 4.05 (t, 1 H, J = 8.0 Hz), 3.22 (dd, 1 H, J = 14.9, 7.3 Hz), 3.00 (dd, 1 H, J = 14.9, 8.2 Hz), 1.90 (m, 2 H), 1.70-1.18 (complex, 4 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.86 (d, 3 H, J = 6.5 Hz), 0.85 (m, 2 H); ^{13}C NMR δ 171.2, 150.6, 149.5, 145.3, 143.6, 140.2, 132.6, 131.1, 128.3, 128.0, 127.8, 127.7, 126.3, 125.5, 125.2, 124.7, 115.2, 76.1, 50.2, 46.1, 41.6, 39.9, 37.9, 34.4, 31.3, 27.7, 27.0, 25.1, 21.7; HRMS *m/z* calcd for $C_{33}H_{37}NO_4$: 511.2722, found: 511.2717.

Anal. Calcd for $C_{33}H_{37}NO_4$: C, 77.50; H, 7.24. Found: C, 77.21; H, 7.37.

1,1-Dimethoxyheptan-6-one (17). The general procedure of Hudlicky and Ranu[77] was followed. A solution of 29.1 g (0.30 mol) of 1-methylcyclohexene (**16**) was taken in 150 mL of MeOH and 75 mL of CH_2Cl_2 and ozonized at -78 °C until a blue color persisted. The solution was degassed with N_2, and 75 g of dimethyl sulfide and 0.75 g *p*-toluenesulfonic acid was added to it. The reaction mixture was allowed to warm to room temperature and was stirred for 8 h. The reaction mixture was then diluted with 75 mL of

CH_2Cl_2 and washed with 10 mL of 2 *M* HCl, 20 mL of H_2O, 20 mL of NaCl, then dried ($MgSO_4$). Concentration gave an oil which was vacuum distilled using a bleed valve (boiling range 45-50 °C, 50mm) to give 47.0 g (0.27 mol, 90%) of pure 1,1-dimethoxyheptan-6-one (**17**) which had the following spectral properties. IR 1710 cm^{-1}; ^1H NMR δ 4.2 (t, 1 H, J = 6 Hz), 3.2 (s, 6 H), 2.4 (t, 2 H, J = 6 Hz), 2.0 (s, 3 H), 1.2 (m, 6 H); ^{13}C NMR δ 171.3, 101.9, 50.1, 48.9, 31.2, 29.5, 29.0, 17.8.

2-Methyl-1-cyclopentenecarboxaldehyde (19). To a stirred solution of 25 g (142 mmol) of **17** in 250 mL of THF, cooled to 0 °C, was added 250 mL of 3% $HClO_4$ dropwise over 30 min. The reaction was stirred at 0 °C for 4 h and another 4 h at room temperature. Upon completion, the reaction mixture was diluted with 100 mL of CH_2Cl_2, washed with 15 mL of 5% $NaHCO_3$. The organic layer was separated and washed with 15 mL of NaCl, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield 14.0 g (107 mmol, 76%) of the 6-ketoheptanal (**18**), which was immediately converted to its enamine. To a stirred ice cold solution of **18** in 150 mL anhydrous ether was added dropwise over a period of 30 min, 17.0 g (19.8 mL, 0.20 mol) of freshly distilled piperidine. After completion of the addition, the reaction was stirred at 0 °C for 4 h, and the resulting solution was washed with 15 mL of NaCl, then dried ($MgSO_4$), and concentrated. The enamine was cyclized using 150 mL of diethyl ether and acetic acid at reflux for 8 h to yield 7.68 g (69.8 mmol, 65%) of **19** as an oil which had the following properties. IR 2722, 1666 cm^{-1}; ^1H NMR δ 10.00 (s, 1 H), 2.60-2.52 (t, 4 H, J = 7.0 Hz), 2.14 (s, 3 H), 1.86 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 188.4, 162.6, 138.0, 40.8, 30.0, 21.1, 14.2.

2-Methylcyclopentene-1-methanol (20). The procedure of Ziegler, Nangia, and Schulte[78] was followed. To a stirred solution of 7.68 g (69.8 mmol) of crude **19** in 250 mL of dry ether at -78 °C was added 4.60 g (0.12 mol) of $LiAlH_4$ in small portions over 20 min. After the addition was complete, the reaction was maintained at -78 °C for 15 min and then allowed to warm to 0 °C. After 1 h at 0 °C, the reaction mixture was decomposed by the slow addition of 5.0 mL of H_2O, 4.5 mL of 15% aqueous NaOH, and 10 mL of H_2O. Separation of the ether layer was followed by extraction of the aqueous layer with 20 mL portions of ether (2x). The ether layers were combined, washed with 25 mL of NaCl, then dried ($MgSO_4$), and concentrated under reduced pressure to give a light oil. This oil was vacuum distilled (boiling range 54-58 °C, 1 mm) to give 7.00 g (62.4 mmol, 89%) of **20** as the average yield of three runs. The spectral properties of **20** were as follows. IR 3332, 2954, 2926, 2852, 1010 cm^{-1}; ^1H NMR δ 4.18 (s, 2 H), 2.44 (m, 2 H), 2.32 (m, 2 H), 1.81 (quintet, 2 H, J = 7.5 Hz), 1.68 (s, 3 H), 1.32 (s, 1 H); ^{13}C NMR δ 136.0, 134.0, 59.2, 38.7, 34.1, 21.5, 13.7.

2-Methylcyclopentene-1-methylbromide (21). The procedure of Ziegler, Nangia, and Schulte[78] was followed. To a stirred solution of 7.00 g (62.4 mmol) of **20** in 70 mL of pentane was added dropwise 10.0 mL of 48% HBr at 0 °C with constant stirring over a period of 10 min. On completion of addition, the reaction was stirred for a further 30 min, diluted with 20 mL of diethyl ether, and washed successively with 15 mL of $NaHCO_3$, 15 mL of NaCl, and then dried ($MgSO_4$). Concentration yielded 8.29 g (47.4 mmol, 76%) of bromide **21** which was used immediately for alkylation without further purification. The spectral properties of **21** were as follows. IR 2965, 2909, 2864, 1664

cm^{-1}; ^1H NMR δ 4.09 (s, 2 H), 2.47 (m, 2 H), 2.34 (m, 2 H), 1.83 (quintet, 2 H, J = 7.4 Hz), 1.70 (s, 3 H); ^{13}C NMR δ 139.8, 131.3, 38.9, 34.5, 30.0, 21.2, 14.0.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-3-(2-Methyl-1-cyclopentenyl)-2-(2-nitro phenyl)-4-pentenoate (27). 1.40 g (2.86 mmol, 76%); $[\alpha]_D^{23}$ = -52.2° (*c* = 0.23, $CHCl_3$); IR 1728, 1530, 1349 cm^{-1}; ^1H NMR δ 7.83 (dd, 1 H, J = 8.2, 1.2 Hz), 7.63 (dd, 1 H, J = 8.0, 1.5 Hz), 7.54 (td, 1 H, J = 7.5, 1.3 Hz), 7.36 (ddd, 1 H, J = 8.1, 7.2, 1.5 Hz), 7.15 (m, 4 H), 7.10 (m, 1 H), 4.79 (td, 1 H, J = 10.7, 4.6 Hz), 4.00 (t, 1 H, J = 7.7 Hz), 2.62 (dd, 1 H, J = 14.1, 6.8 Hz), 2.52 (dd, 1 H, J = 13.7, 7.7 Hz), 2.14 (m, 4 H), 1.93 (m, 2 H), 1.66 (m, 2 H), 1.66 (m, 2 H), 1.56 (s, 3 H), 1.55-1.39 (complex, 4 H), 1.10 (s, 3 H), 1.07 (s, 3 H), 0.87 (d, 3 H, J = 6.6 Hz), 0.85 (m, 2 H); ^{13}C NMR δ 171.9, 150.8, 149.7, 134.9, 133.3, 132.4, 131.0, 130.5, 127.8, 127.7, 125.4, 125.3, 124.5, 75.8, 50.2, 44.8, 41.6, 39.8, 38.3, 35.6, 34.4, 32.8, 31.3, 27.0, 26.9, 25.9, 21.8, 21.6, 13.7; HRMS *m/z* calcd for $C_{31}H_{39}NO_4$: 489.2879, found: 489.2882.

Anal. Calcd for $C_{31}H_{39}NO_4$: C, 76.07; H, 7.98. Found: C, 75.79; H, 8.07.

Representative Ozonolysis Procedure for the Preparation of Nitro Ketone Esters: (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-2-(2-Nitrophenyl)-4-oxopentanoate (30). A solution of 800 mg (1.78 mmol) of **23** in 75 mL of MeOH was ozonized at -78 °C until TLC indicated complete consumption of starting material. Excess ozone was purged with a stream of dry N_2, and 5.08 g (6.00 mL, 84.9 mmol) of dimehtyl sulfide was added. The mixture was allowed to warm to 0 °C and 200 mg of *p*-toluenesulfonic was added. The solution was stirred at 0 °C for 1 h and then was warmed to room temperature with stirring for 8 h. The reaction was concentrated, diluted with 50 mL of ether, washed with 15 mL of $NaHCO_3$ and 15 mL of NaCl, then dried ($MgSO_4$). Concentration yielded 680

mg (1.50 mmol, 84%) of **30** as a yellow oil which was used without further purification. $[\alpha]_D^{23}$ = -81.6° (*c* = 0.39, $CHCl_3$); IR 1729, 1530, 1355 cm^{-1}; ^1H NMR δ 7.90 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.51 (m, 2 H), 7.38 (ddd, 1 H, *J* = 8.2, 6.6, 2.2 Hz), 7.27-7.12 (complex, 4 H), 7.10 (td, 1 H, *J* = 7.6, 1.7 Hz), 4.79 (td, 1 H, *J* = 10.7, 4.4 Hz), 4.23 (t, 1 H, *J* = 6.5 Hz), 2.94 (dd, 1 H, *J* = 18.4, 6.8 Hz), 2.81 (dd, 1 H, *J* = 18.4, 6.4 Hz), 2.09 (s, 3 H), 1.99 (m, 2 H), 1.59-1.36 (complex, 4 H), 1.05 (s, 3 H), 0.95 (s, 3 H), 0.88 (d, 3 H, *J* = 6.5 Hz) 0.84 (m, 2 H); ^{13}C NMR δ 205.1, 171.0, 151.2, 149.1, 133.0, 132.9, 132.6, 128.2, 127.9, 125.3, 125.2, 125.0, 76.6, 50.2, 45.9, 42.8, 41.2, 39.7, 34.5, 31.3, 29.7, 26.8, 26.2 (2), 21.8; HRMS *m/z* calcd for $C_{27}H_{33}NO_5$: 451.2358, found: 451.2354.

Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.84; H, 7.32. Found: C, 71.70; H, 7.37.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-2-(2-Nitrophenyl)-4-oxooctanoate (31). 542 mg (1.10 mmol, 88%); $[\alpha]_D^{23}$ = -86.3° (*c* = 0.45, $CHCl_3$); IR 1722, 1532, 1354 cm^{-1}; ^1H NMR δ 7.88 (d, 1 H, *J* = 8.0 Hz), 7.51 (m, 2 H), 7.36 (ddd, 1 H, J = 8.2, 6.5, 2.5 Hz), 7.26 (complex, 5 H), 4.79 (dt, 1 H, *J* = 10.6, 4.3 Hz), 4.25 (t, 1 H, *J* = 6.5 Hz), 2.93 (dd, 1 H, *J* = 18.1, 6.9 Hz), 2.78 (dd, 1 H, *J* = 18.1, 6.5 Hz), 2.32 (m, 2 H), 1.97 (m, 2 H), 1.58-1.38 (complex, 5 H), 1.38-1.19 (complex, 3 H), 1.04 (s, 3 H), 0.95 (s, 3 H), 0.88 (t, 3 H, *J* = 7.2 Hz), 0.87 (d, 3 H, *J* = 6.5 Hz), 0.83 (m, 2 H); ^{13}C NMR δ 207.5, 170.9, 151.1, 149.1, 132.8 (2), 131.2, 128.1, 127.8, 125.2, 125.1, 124.8, 76.3, 50.2, 44.9, 42.7, 42.1, 41.1, 39.6, 34.4, 31.2, 29.6, 26.8, 26.1, 25.7, 22.1, 21.7, 13.7; HRMS *m/z* calcd for $C_{30}H_{39}NO_5$: 493.2828, found: 493.2824.

Anal. Calcd for $C_{30}H_{39}NO_5$: C, 73.02; H, 7.91. Found: C, 72.87; H, 7.99.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-5,5-Dimethyl-(2-nitrophenyl)-4-oxohexanoate

(32). 520 mg (1.05 mmol, 87%); $[\alpha]_D^{23}$ = -111.1° (*c* = 0.39, $CHCl_3$); mp 134-136 °C; IR 1731, 1705, 1529, 1357 cm^{-1}; ^1H NMR δ 7.88 (dd, 1 H, *J* = 8.2, 1.1 Hz), 7.51 (m, 2H), 7.37 (ddd, 1 H, *J* = 8.2, 6.6, 2.2 Hz) 7.26-7.08 (complex, 5 H), 4.79 (td, 1 H, *J* = 10.6, 4.1 Hz), 4.25 (t, 1 H, *J* = 6.5 Hz), 3.00 (dd, 1 H, *J* = 18.2, 7.0 Hz), 2.92 (dd, 1 H, *J* = 18.2, 6.2 Hz), 2.03 (dm, 1 H, *J* = 12.4 Hz), 1.93 (td, 1 H, *J* = 11.3, 3.0 Hz), 1.71-1.36 (complex, 4 H), 1.08 (s, 9 H), 1.04 (s, 3 H), 0.93 (s, 3 H), 0.89 (d, 3 H, *J* = 6.5 Hz), 0.84 (m, 2 H); ^{13}C NMR δ 212.4, 171.3, 151.1, 149.5, 132.9 (2), 131.1, 128.2, 127.9, 125.3, 125.1, 124.9, 76.4, 50.3, 43.8, 42.8, 41.2, 39.9, 39.7, 34.5, 31.3, 26.9, 26.6, 26.3 (3), 25.7, 21.7; HRMS *m/z* calcd for $C_{30}H_{39}NO_5$: 493.2828, found: 493.2827.

Anal. Calcd for $C_{30}H_{39}NO_5$: C, 73.02; H, 7.91. Found: C, 72.93; H, 7.96

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*)-2-(2-Nitrophenyl)-4-oxo-4-phenylpentanoate (33). 550 mg (1.07 mmol, 89%); $[\alpha]_D^{23}$ = -57.4° (*c* = 0.59, $CHCl_3$); IR 1728, 1688, 1530, 1355 cm^{-1}; ^1H NMR δ 7.90 (m, 3 H), 7.62-7.52 (complex, 3 H), 7.48-7.35 (complex, 3 H), 7.18 (m, 4 H), 6.99 (m, 1 H), 4.83 (td, 1 H, *J* = 10.7, 4.3 Hz), 4.43 (t, 1 H, *J* = 6.5 Hz), 3.44 (dd, 1 H, *J* = 18.4, 6.5 Hz), 3.36 (dd, 1 H, *J* = 18.4, 6.5 Hz), 2.07 (dm, 1 H, *J* = 12.4 Hz), 1.98 (td, 1 H, *J* = 11.3, 3.3 Hz), 1.61-1.40 (complex, 4 H), 1.06 (s, 3 H), 1.00 (s, 3 H), 0.89 (d, 3 H, *J* = 6.5 Hz), 0.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.5, 171.0, 151.9, 149.1, 136.2, 133.2, 133.1, 132.9, 131.6, 128.4, 128.2, 127.9 (2), 127.8, 125.2, 124.9, 76.4, 50.1, 43.0, 41.3, 41.1, 39.5, 34.4, 31.2, 26.7, 26.4, 25.8, 21.7; HRMS *m/z* calcd for $C_{32}H_{35}NO_5$: 513.2515, found: 513.2512.

Anal. Calcd for $C_{32}H_{35}NO_5$: C, 74.85; H, 6.82. Found: C, 74.73; H, 6.91.

Representative Preparation of Tetrahydroquinoline-4-carboxylic Esters: (1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*S*,4*R*)-2-Methyl-1,2,3,4-tetrahydroquinoline-4-car-

boxylate (36). To a solution of mg 500 mg (1.10 mmol) of 30 in 150 mL of MeOH was added 125 mg of 5% Pd/C, and the mixture was shaken under 4 atm of H_2 at 30 °C for 4 h. The solvent was removed under reduced pressure, the residue was diluted with 50 mL of ether, and the solution was filtered through a pad of Celite topped with a layer of anhydrous $MgSO_4$ to separate the catalyst. Concentration gave the crude product as a single isomer by ^1H and ^{13}C NMR spectroscopy. Final purification on four 20 cm x 20 cm PTLC plates eluted with hexane:ether (95:5) gave 365 mg (0.90 mmol, 82%) of 36 as a light yellow oil, $[\alpha]_D^{23} = -13.2°$ (c = 0.45, $CHCl_3$); IR 3383, 1720cm^{-1}; ^1H NMR δ 7.38-7.23 (complex, 4 H), 7.09 (m, 1 H), 7.00 (m, 2 H), 6.67 (m, 1 H), 6.47 (dd, 1 H, J = 8.2, 1.2 Hz), 4.91 (td, 1 H, J = 10.7, 4.3 Hz), 3.66 (br s, 1 H), 3.33 (dd, 1 H, J = 11.9, 5.9 Hz), 3.27 (m, 1 H), 2.02 (td, 1 H, J = 12.1, 1.6 Hz), 1.84 (m, 2 H), 1.60 (t, 2 H, J = 11.2 Hz), 1.60-1.33 (complex, 3 H), 1.38 (s, 3 H), 1.26 (s, 3 H), 1.15 (d, 3 H, J = 6.2 Hz), 0.87 (m, 2 H), 0.85 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 173.5, 151.6, 144.7, 129.3, 127.9, 127.6, 125.4, 125.1, 117.9, 117.3, 114.5, 74.7, 50.1, 46.6, 43.4, 41.3, 39.8, 34.5, 34.2, 31.2, 27.1, 26.7, 26.1, 22.2, 21.8; HRMS *m/z* calcd for $C_{27}H_{35}NO_2$: 405.2668, found: 405.2666.

Anal. Calcd for $C_{27}H_{35}NO_2$: C, 80.00; H, 8.64. Found: C, 79.78; H, 8.72.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*S*,4*R*)-2-Butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (37). 250 mg (0.56 mmol, 88%); $[\alpha]_D^{23} = +11.6°$ (c = 3.03, $CHCl_3$); IR 3406, 1716 cm^{-1}; ^1H NMR δ 7.36-7.20 (complex, 4 H), 7.10 (m, 1 H), 6.99 (m, 2 H), 6.66 (t, 1 H, J = 7.4 Hz), 6.47 (dd, 1 H, J = 8.2, 1.2 Hz), 4.90 (td, 1 H, J = 10.6, 4.4 Hz), 4.12 (br s, 1 H), 3.31 (dd, 1 H, J = 11.9, 6.2 Hz), 3.11 (m, 1 H), 2.03 (m, 2 H), 1.88 (m, 2 H), 1.80-1.19 (complex, 10 H), 1.38 (s, 3 H), 1.26 (s, 3 H), 0.92 (t, 3 H, J = 6.8 Hz), 0.87 (m, 2 H), 0.85 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 173.6, 151.5, 144.7, 129.3, 127.9, 127.6,

125.4, 125.1, 118.1, 117.2, 114.5, 74.8, 51.0, 50.1, 43.4, 41.3, 39.8, 36.0, 34.5, 32.4, 31.2, 27.7, 27.0, 26.7, 26.3, 22.7, 21.7, 14.0; HRMS *m/z* calcd for $C_{30}H_{41}NO_2$: 447.3137, found: 447.3138.

Anal. Calcd for $C_{30}H_{41}NO_2$: C, 80.53; H, 9.17. Found: C, 80.40; H, 9.21.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*,4*R*)-2-*tert*-Butyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (38). 220 mg (0.49 mmol, 87%); $[\alpha]_D^{23}$ = +10.0° (*c* = 0.45, $CHCl_3$); IR 3380, 1719 cm^{-1}; ^1H NMR δ 7.37-7.23 (complex, 4 H), 7.11 (m, 1 H), 7.03 (m, 2 H), 6.65 (td, 1 H, *J* = 7.6, 1.3 Hz), 6.50 (dd, 1 H, *J* = 8.0, 1.0 Hz), 4.92 (td, 1 H, *J* = 10.8, 4.4 Hz), 3.80 (br s, 1 H), 3.37 (dd, 1 H, *J* = 12.5, 5.3 Hz), 2.88 (dd, 1 H, *J* = 11.3, 2.2 Hz), 1.97 (m, 3H), 1.80-1.20 (complex, 5 H), 1.39 (s, 3 H), 1.29 (s, 3 H), 0.95 (s, 9 H), 0.87 (m, 2 H), 0.86 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 173.9, 151.2, 145.2, 128.7, 127.9, 127.6, 125.4, 125.1, 118.2, 117.0, 114.6, 74.9, 60.0, 50.2, 44.1, 41.2, 40.0, 34.4, 33.2, 31.2, 27.8, 27.4, 26.8, 26.0, 25.8 (3), 21.8; HRMS *m/z* calcd for $C_{30}H_{41}NO_2$: 447.3137, found: 447.3134.

Anal. Calcd for $C_{30}H_{41}NO_2$: C, 80.53; H, 9.17. Found: C, 80.38; H, 9.27.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (2*R*,4*R*)-2-Phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate (39). 397 mg (0.85 mmol, 79%); $[\alpha]_D^{23}$ = +35.1° (*c* = 2.02, $CHCl_3$); IR 3383, 1724 cm^{-1}; ^1H NMR δ 7.39-7.21 (m, 10 H), 7.04 (m, 2 H), 6.72 (td, 1 H, *J* = 7.5, 1.2 Hz), 6.52 (dd, 1 H, *J* = 7.8, 1.4 Hz), 4.87 (td, 1 H, *J* = 10.8, 4.4 Hz), 4.25 (dd, 1 H, *J* = 10.1, 3.5 Hz), 3.93 (br s, 1 H), 3.42 (dd, 1 H, *J* = 11.2, 6.5 Hz), 1.97 (m, 3 H), 1.76 (dm, 1 H, *J* = 12.5 Hz), 1.61 (m, 2 H), 1.42 (m, 2 H), 1.37 (s, 3 H), 1.24 (s, 3 H), 0.86 (m, 2 H), 0.81 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR δ 173.3, 151.6, 144.9, 143.4, 129.5, 128.7, 127.9 (2), 127.8, 126.7, 125.4, 125.1, 117.7 (2), 114.7, 74.8, 56.1, 50.1, 43.7, 41.2, 39.8, 35.3, 34.5, 31.2, 27.5, 26.6, 25.8, 21.8; HRMS *m/z* calcd for $C_{32}H_{37}NO_2$: 467.2824, found: 467.2826.

Anal. Calcd for $C_{32}H_{37}NO_2$: C, 82.22; H, 7.92. Found: C, 82.18; H, 7.93.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (4*R*)-1,2,3,4-tetrahydroquinoline-4-carboxylate (35). A solution of 800 mg (1.84 mmol) of **22** in 150 mL of MeOH was treated with ozone, dimethyl sulfide, and *p*-toluenesulfonic as described for the preparation of **30**. The reaction was concentrated, diluted with 50 mL of ether, washed with 15 mL of $NaHCO_3$ and 10 mL of NaCl, then dried ($MgSO_4$). Evaporation of the ether gave acetal **28** contaminated with a small amount of aldehyde **29**. This mixture was dissolved in 50 mL of THF and 50 mL of 7% aqueous $HClO_4$ was added dropwise at 0 °C. The solution was stirred at 0 °C for 1 h and at room temperature for 12 h. It was then extracted with 20 mL of CH_2Cl_2 (2x). The combined organic layers were washed with 10 mL of $NaHCO_3$ and 10 mL of NaCl, then dried ($MgSO_4$). Concentration gave 691 mg (1.58 mmol, 86%) of **29** which was used without further purification: $[\alpha]_D^{23}$ = -15.8° (*c* = 0.33, $CHCl_3$); IR 2855, 2728, 1733, 1535, 1353 cm^{-1}; ^1H NMR δ 9.49 (t, 1 H, *J* = 0.8 Hz), 7.94 (dd, 1 H, *J* = 8.1, 1.4 Hz), 7.58 (td, 1 H, J = 7.8, 1.4 Hz), 7.43 (m, 2 H), 7.24 (m, 4 H), 7.13 (m, 1 H), 4.81 (td, 1 H, *J* = 10.7, 4.4 Hz), 4.15 (t, 1 H, *J* = 6.7 Hz), 2.88 (ddd, 1 H, *J* = 18.7, 6.5, 0.8 Hz), 2.78 (ddd, 1 H, *J* = 18.7, 6.9, 0.8 Hz), 2.00 (m, 2 H), 1.63 (m, 3 H), 1.43 (m, 1 H), 1.08 (s, 3 H), 1.04 (s, 3H), 0.89 (d, 3 H, *J* = 6.6 Hz), 0.83 (m, 2 H); ^{13}C NMR δ 198.8, 170.4, 151.6, 149.0, 133.2, 132.5, 131.5, 128.5, 128.0, 125.4, 125.2 (2), 76.4, 50.2, 46.2, 41.9, 41.3, 39.5, 34.5, 31.3, 27.5, 26.6, 24.8, 21.8.

To a solution of 500 mg (1.14 mmol) of **29** in 150 mL of MeOH was added 125 mg of 5% Pd/C, and the mixture was shaken under 4 atm of H_2 at 30 °C for 8 h. The solvent was removed under reduced pressure, and the residue was diluted with 20 mL of ether. The solution was filtered through a pad of Celite topped with a layer of anhydrous

$MgSO_4$ to separate the catalyst. Concentration gave a yellow oil that was pure by ^1H and ^{13}C NMR spectroscopy. Final purification on four 20 cm x 20 cm PTLC plates eluted by hexane:ether (95:5) gave 376 mg (0.96 mmol, 84%) of **35** as a colorless oil: $[\alpha]_D^{23}$ = +43.7° (*c* = 0.87, $CHCl_3$); IR 3411, 1722 cm^{-1}; ^1H NMR δ 7.30 (m, 4 H), 7.12 (m, 1 H), 6.99 (m, 2 H), 6.64 (td, 1 H, *J* = 7.6, 1.0 Hz), 6.44 (dd, 1 H, *J* = 8.2, 0.8 Hz), 4.83 (td, 1 H, *J* = 10.7, 4.4 Hz), 3.82 (br s, 1 H), 3.14 (m, 3 H), 2.01 (m, 1 H), 1.92-1.70 (complex, 3 H), 1.60 (d, 2 H, *J* = 11.3 Hz), 1.42 (m, 2 H), 1.29 (s, 3 H), 1.21 (s, 3 H), 0.87 (m, 2 H), 0.84 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 173.2, 151.4, 144.2, 130.8, 127.9 (2), 125.4, 125.1, 117.4, 116.8, 114.4, 74.6, 50.2, 42.1, 41.5, 39.8, 38.9, 34.5, 31.2, 27.1, 26.6, 25.9, 24.5, 21.8; HRMS *m/z* calcd for $C_{26}H_{33}NO_2$: 391.2511, found: 391.2510.

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.80; H, 8.44. Found: C, 79.69; H, 8.51.

(1*R*,2*S*,5*R*)-8-Phenylmenthyl (1*S*,4a*S*,6*R*)-1-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-carboxylate (40). A solution of 1.20 g (2.45 mmol) of **27** in 150 mL of MeOH was treated with ozone, dimethyl sulfide, and *p*-toluenesulfonic acid as described for the preparation of **30**. Workup gave an oil that was flash chromatographed on silica gel using increasing concentrations of ether in hexane. Concentration gave 1.10 g (2.11 mmol, 86%) of **34** as a light yellow oil which was used without further purification, $[\alpha]_D^{23}$ = -40.6° (*c* = 1.65, $CHCl_3$); IR 1716, 1530, 1353 cm^{-1}; ^1H NMR δ 7.90 (dd, 1 H, *J* = 8.1, 1.2 Hz), 7.49 (m, 2 H), 7.38 (ddd, 1 H, J = 8.2, 7.1, 1.8 Hz), 7.26-7.07 (complex, 5 H), 4.78 (td, 1 H, *J* = 10.8, 4.1 Hz), 4.26 (t, 1 H, *J* = 6.8 Hz), 2.93 (dd, 1 H, *J* = 18.2, 7.1 Hz), 2.77 (dd, 1 H, *J* = 18.2, 6.2 Hz), 2.42 (t, 2 H, *J* = 7.1 Hz), 2.35 (m, 2 H), 2.12 (s, 3 H), 1.95 (m, 2 H), 1.80 (quintet, 2 H, *J* = 7.1 Hz), 1.60-1.34 (complex, 4 H), 1.04 (s, 3 H), 0.93 (s, 3 H), 0.88 (d, 3 H, *J* = 6.5 Hz), 0.84 (m, 2 H); ^{13}C NMR δ

208.1, 206.8, 171.0, 151.1, 149.7, 133.0, 132.7, 131.2, 128.3, 127.9, 125.4, 125.2, 125.0, 76.6, 50.2, 45.0, 42.7, 42.3, 41.2, 39.7, 34.5, 31.3, 29.9, 29.8, 26.9, 26.4, 25.9, 21.8, 17.6.

To a solution of 912 mg (1.75 mmol) of **34** in 150 mL of MeOH was added 225 mg of 5% Pd/C, and the mixture was hydrogenated as described for **36**. Workup gave a light yellow oil which was a single isomer by ^{1}H and ^{13}C NMR spectroscopy. This oil was purified on five 20 cm x 20 cm PTLC plates eluted with hexane:ether (95:5) to give 679 mg (1.49 mmol, 85%) of **40** as a colorless oil, $[\alpha]_D^{23} = +39.2^{\circ}$ (c = 2.60, $CHCl_3$); IR (thin film) 1724 cm^{-1}; ^{1}H NMR δ 7.26 (m, 4 H), 7.11 (m, 2 H), 7.00 (t, 1 H, J = 7.2 Hz), 6.69 (t, 1 H, J = 7.5 Hz), 6.66 (d, 1 H, J = 8.2 Hz), 4.88 (td, 1 H, J = 10.9, 4.4 Hz), 3.44 (q, 1 H, J = 4.6 Hz), 3.31 (distorted t, 1 H, J = 7.5 Hz), 2.99 (m, 1 H), 1.97 (m, 3 H), 1.73 (m, 3 H), 1.62-1.42 (complex, 8 H), 1.27 (s, 3 H), 1.22 (s, 3 H), 1.19 (d, 3 H, J = 6.2 Hz), 0.87 (m, 2 H), 0.85 (d, 3 H, J = 6.5 Hz); ^{13}C NMR δ 173.4, 151.6, 146.9, 128.5, 127.9, 127.5, 125.5, 125.1, 124.0, 117.0, 112.9, 75.0, 53.1, 50.2, 50.0, 44.1, 41.6, 39.9, 34.6 (2), 31.5, 31.2, 30.0, 26.8, 26.6 (2), 21.8, 21.1, 18.5; HRMS *m/z* calcd for $C_{31}H_{41}NO_2$: 459.3137, found: 459.3135.

Anal. Calcd for $C_{31}H_{41}NO_2$: C, 81.05; H, 8.93. Found: C, 80.86; H, 9.05.

(+)-(1*S*,4a*S*,6*R*)-1-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-6-methanol (41). To a stirred solution of 160 mg (0.35 mmol) of **40** in 25 mL of anhydrous THF was added 13 mg (0.35 mmol) $LiAlH_4$, and the reaction was stirred at room temperature for 4 h, and then was quenched by addition of 10 mL of cold saturated Na_2SO_4 solution and filtered. The filtrate was diluted with 25 mL of H_2O and extracted with 50 mL portions of ether (3x). The ether extracts were combined and washed with 15 mL of NaCl, dried ($MgSO_4$), and concentrated to give a colorless oil which was purified

by PTLC using hexane:ether (50:50) to afford 65 mg (0.28 mmol, 81%) of **41**, $[\alpha]_D^{23}$ = +62.9° (*c* = 0.35, $CHCl_3$); IR 3378 cm^{-1}; ^1H NMR δ 7.16-7.08 (complex, 2 H), 6.79 (m, 2 H), 3.90 (dd, 1 H, *J* = 10.3, 4.6 Hz), 3.82 (dd, 1 H, *J* = 10.3, 4.4 Hz), 3.34 (m, 2 H), 2.98 (m, 2 H), 2.23 (ddd, 1 H, *J* = 13.4, 8.0, 5.7 Hz), 2.00 (m, 1 H), 1.88 (m, 1 H), 1.80-1.70 (complex, 2 H), 1.63-1.39 (complex, 3 H), 1.25 (d, 3 H, *J* = 5.9 Hz); ^{13}C NMR δ 148.3, 129.8, 127.3, 127.0, 119.0, 114.2, 68.1, 55.7, 50.4, 39.1, 36.5, 32.9, 31.9, 21.6, 20.0; HRMS *m/z* calcd for $C_{15}H_{21}NO$: 231.1623, found: 231.1624.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.92; H, 9.09. Found: C, 77.75; H, 9.12.

(1*R*,2*S*,5*R*)-8-Phenylmenthol (66 mg, 0.28 mmol, 82%) was also recovered from the reaction, $[\alpha]_D^{23}$ = -26.4° (*c* = 2.00, C_2H_5OH).

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CRYSTAL DATA AND STRUCTURE REFINEMENT FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDROBENZO[*c*]THIOPHENE-1-ACETIC ACID (39)**

Empirical formula	$C_{10}H_{16}O_2S$
Formula weight	200.29
Temperature	293 (2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2/c
Unit cell dimensions	a = 7.164 (3) A alpha = 90 deg
	b = 13.735 (4) A beta = 91.24 deg
	c = 21.708 (8) A gamma = 90 deg
Volume	2135.5 (13) A^{-3}
Z, Calculated density	8, 1.246 Mg/m^{-3}
Absorption coefficient	0.270 mm^{-1}
F (000)	864
Crystal size	0.1 x 0.1 x 0.5 mm
Theta range for data collection	1.75 to 21.26 deg.
Index ranges	-1<=h<=7, -14<=k<=1, -22<=l<=22
Reflections collected / unique	3386 / 2361 [R(int) = 0.0655]
Completeness to 2theta = 21.26	94.3%
Refinement method	Full-matrix least-sqaures on F^2
Data / restraints / parameters	2361 / 0 / 236
Goodness-of-fit on F^2	0.991
Final R indices [I > 2 sigma(I)]	R1 = 0.0658, wR2 = 0.1372
R indices (all data)	R1 = 0.1353, wR2 = 0.1647
Extinction coefficient	0.0000(9)
Largest diff. Peak and hole	0.380 and –0.221e.A^{-3}

ATOMIC COORDINATES AND EQUIVALENT ISOTROPIC DISPLACEMENT PARAMETERS FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDROBENZO-[*c*]THIOPHENE-1-ACETIC ACID (39)**

	X	Y	z	U (eq)
C(1)	-445(11)	4045(5)	3372(3)	58(2)
S(2)	-302(5)	3138(2)	3976(1)	111(1)
C(3)	1996(14)	3512(6)	4209(4)	96(3)
C(3')	2746(10)	4246(5)	3741(3)	57(2)
C(4)	4278(12)	4896(7)	3988(3)	88(3)
C(5)	3533(14)	5659(6)	4430(3)	86(3)
C(6)	1931(15)	6205(6)	4173(4)	102(3)
C(7)	389(12)	5541(6)	3974(4)	78(3)
C(7')	1073(10)	4793(5)	3507(3)	50(2)
C(8)	-241(10)	3600(5)	2734(3)	51(2)
C(9)	-1671(11)	2829(6)	2601(3)	50(2)
O(1)	-1320(7)	1995(4)	2494(2)	64(2)
O(2)	-3390(8)	3175(3)	2610(2)	74(2)
C(91)	4684(10)	70(5)	3432(3)	55(2)
S(92)	4739(4)	999(2)	4031(1)	93(1)
C(93)	7060(12)	662(5)	4293(3)	78 3)
C(93')	7865(10)	-35(5)	3823(3)	58(2)
C(94)	9481(11)	-644(7)	4075(3)	79(3)
C(95)	8811(13)	-1418(6)	4524(3)	82(3)
C(96)	7304(15)	-2030(6)	4244(4)	96(3)
C(97)	5693(12)	-1412(6)	4048(3)	72(2)
C(97')	6268(10)	-641(5)	3581(3)	50(2)
C(98)	4839(10)	500(5)	2791(3)	51(2)
C(99)	3340(11)	1226(6)	2654(3)	48(2)
O(91)	1635(7)	900(3)	2732(2)	67(2)
O(92)	3674(7)	2032(4)	2465(2)	69(2)

BOND LENGTHS (Å) FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDRO-BENZO[*c*]THIOPHENE-1-ACETIC ACID (39)**

Bond Length	Å
C(1) – C(7)	1.521(9)
C(1) – C(8)	1.524(8)
C(1) – S(2)	1.811(6)
S(2) – C(3)	1.787(9)
C(3) – C(3')	1.537(10)
C(3') - C(7')	1.495(9)
C(3') - C(4)	1.505(10)
C(4) – C(5)	1.524(11)
C(5) – C(6)	1.471(11)
C(6) – C(7)	1.489(11)
C(7) – C(7')	1.532(9)
C(8) – C(9)	1.497(9)
C(9) – O(1)	1.196(7)
C(9) – O(2)	1.321(8)
C(91) - C(98)	1.591(8)
C(91) - C(97')	1.526(9)
C(91) - S(92)	1.820(6)
S(92) - C(93)	1.806(8)
C(93) - C(93')	1.521(10)
C(93') - C(97')	1.500(9)
C(93') - C(94)	1.521(9)
C(94) - C(95)	1.527(10)
C(95) - C(96)	1.488(11)
C(96) - C(97)	1.487(10)
C(97) - C(97')	1.530(9)
C(98) - C(99)	1.490(9)
C(99) - O(92)	1.206(8)
C(99) - O(91)	1.315(8)

BOND ANGLES FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDRO-BENZO[*c*]THIOPHENE-1-ACETIC ACID (39)**

Bond	Angle (°)
C(7) - C(1) – C(8)	111.3(6)
C(7') - C(1) - S(2)	107.2(5)
C(8) - C(1) – S(2)	112.2(5)
C(3) - S(2) - C(1)	92.5(4)
C(3') - C(3) - S(2)	109.6(5)
C(7') - C(3') - C(4)	113.3(6)
C(7') - C(3') - C(3)	105.4(7)
C(4) - C(3') - C(3)	114.7(6)
C(3') - C(4) - C(5)	111.7(7)
C(6) - C(5) - C(4)	113.1(7)
C(5) - C(6) - C(7)	111.4(7)
C(6) - C(7) - C(7')	110.9(7)
C(3') - C(7') - C(1)	106.9(6)
C(3') - C(7') - C(7)	112.2(5)
C(1) - C(7') - C(7)	110.1(6)
C(9) - C(8) - C(1)	112.3(6)
O(1) - C(9) - O(2)	123.2(7)
O(1) - C(9) - C(8)	124.7(7)
O(2) - C(9) - C(8)	112.1(6)
C(98) - C(91) – C(97')	111.9(6)
C(98) – C(91) – S(92)	112.4(5)
C(97') - C(91) - S(92)	107.1(4)
C(93) - S(92) – C(91)	92.9(3)
C(93') - C(93) - S(92)	108.1(5)
C(97') - C(93') - C(93)	106.7(6)
C(97') - C(93') - C(94)	112.9(6)
C(93) - C(93') - C(94)	113.7(6)
C(93') - C(94) - C(95)	111.4(7)
C(96) - C(95) – C(94)	111.5(6)
C(97) - C(96) – C(95)	110.2(7)
C(96) - C(97) – C(97')	111.5(7)
C(93') - C(97') - C(91)	106.1(6)
C(93') - C(97') - C(97)	111.4(5)
C(91) - C(97') - C(97)	111.9(6)
C(99) - C(98) – C(91)	112.1(6)
O(92) - C(99) – O(91)	123.2(7)
O(92) - C(99) – C(98)	122.3(8)
O(91) - C(99) – C(98)	114.4(7)

ANISOTRPIC DISPLACEMENT PARAMETERS FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDROBENZO[*c*]THIOPHENE-1-ACETIC ACID (39)**

	U11	U22	U33	U23	U13	U12
C(1)	67(6)	61(5)	47(4)	1(4)	16(4)	-4(5)
S(2)	174(3)	93(2)	65(2)	28(1)	-5(2)	-67(2)
C(3)	151(10)	55(5)	81 (6)	10(5)	-36(6)	16(6)
C(3')	60(6)	61(5)	52(4)	-11(4)	7(4)	10(5)
C(4)	74(6)	132(8)	57(5)	-8(6)	-11(5)	-2(6)
C(5)	110(8)	81(6)	66(6)	-13(5)	-20(6)	-29(6)
C(6)	154(10)	59(6)	92(7)	-21(5)	-27(7)	8(7)
C(7)	85(7)	64(6)	84(6)	-20(5)	-18(5)	20(5)
C(7')	59(5)	37(4)	54(4)	0(3)	-12(4)	-2(4)
C(8)	51(5)	44(4)	57(4)	0(4)	-6(4)	-12(4)
C(9)	43(6)	46(5)	60(5)	3(4)	2(4)	11(5)
O(1)	50(4)	39(3)	100(4)	-13(3)	-11(3)	2(3)
O(2)	51(4)	39(3)	130(5)	7(3)	-9(3)	-1(3)
C(91)	59(5)	52(4)	55(4)	-3(4)	11(4)	9(4)
S(92)	130(2)	85(2)	64(2)	-21(1)	-7(2)	51(2)
C(93)	116(8)	45(5)	72(5)	-3(4)	-13(5)	-1(5)
C(93')	57(5)	64(5)	52(4)	14(4)	3(4)	6(5)
C(94)	54(6)	125(7)	58(5)	3(5)	12(5)	13(6)
C(95)	99(7)	82(6)	62(5)	2(5)	-19(5)	27(6)
C(96)	139(9)	64(6)	86(6)	22(5)	-24(6)	29(7)
C(97)	82(6)	61(5)	72(5)	14(5)	-9(5)	-24(5)
C(97')	55(5)	56(5)	40(4)	-3(4)	0(4)	11(4)
C(98)	61(5)	39(4)	52(4)	-1(3)	2(4)	0(4)
C(99)	54(6)	41(5)	48(4)	-1(4)	-13(4)	0(5)
O(91)	43(3)	36(3)	123(5)	9(3)	-2(3)	0(3)
O(92)	50(4)	52(4)	104(4)	18(3)	-9(3)	-5(3)

HYDROGEN COORDINATES AND ISOTROPIC DISPLACEMENT PARAMETERS FOR (±)-(1*R,3a*R**,7a*S**)-1,3,3a,4,5,6,7,7a OCTAHYDROBENZO-[*c*]THIOPHENE-1-ACETIC ACID (39)**

	x	y	z	U (eq)
H(1A)	-1636	4364	3384	80
H(3A)	2802	2956	4246	80
H(3B)	1946	3826	4604	80
H(3'A)	3224	3870	3407	80
H(4A)	4847	5235	3654	80
H(4B)	5218	4508	4192	80
H(5A)	4507	6094	4566	80
H(5B)	3091	5317	4784	80
H(6A)	2355	6540	3814	80
H(6B)	1516	6682	4462	80
H(7A)	-631	5907	3798	80
H(7B)	-45	5203	4331	80
H(7'A)	1366	5128	3133	80
H(8A)	981	3316	2716	80
H(8B)	-335	4101	2426	80
H(2)	-4319	2642	2625	50
H(91A)	3519	-273	3451	80
H(93A)	7005	340	4684	80
H(93B)	7824	1233	4336	80
H(93C)	8319	351	3489	80
H(94A)	10369	-226	4280	80
H(94B)	10102	-965	3744	80
H(95A)	8322	-1097	4879	80
H(95B)	9837	-1820	4659	80
H(96A)	6919	-2520	4530	80
H(96B)	7781	-2349	3887	80
H(97A)	5225	-1089	4406	80
H(97B)	4711	-1809	3875	80
H(97C)	6614	-963	3208	80
H(98A)	4784	-11	2490	80
H(98B)	6028	817	2763	80
H(91B)	640	1386	2599	50

VITA

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